422 Rec'd PCT/PTO 18 MAY 2000

FORM PTO-1390 (Modified) (REV 10-95) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371	**0769-0420-0X PCT**
	U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR
	09/530965

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/IB98/02154	**18 November 1998**	**21 November 1997**

TITLE OF INVENTION

ALPHA-HYDROXY, -AMINO AND -FLUORO DERIVATIVES OF BETA-SULPHONYL HYDROXAMIC ACIDS AS MATRIX METALLOPROTEINASES INHIBITORS

APPLICANT(S) FOR DO/EO/US

Martha WARPEHOSKI, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   - b. ☒ has been transmitted by the International Bureau.
   - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   - b. ☐ have been transmitted by the International Bureau.
   - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   - d. ☒ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 18 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
    A **SECOND** or **SUBSEQUENT** preliminary amendment.
16. ☐ A substitute specification.
17. ☐ A change of power of attorney and/or address letter.
18. ☐ Certificate of Mailing by Express Mail
19. ☒ Other items or information:

Request for Consideration of Documents Cited in International Search Report
Notice of Priority
PCT/IB/304

PCTUS1/REV03

422 Rec'd PCT/PTO 18 MAY 2000

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 09/530965	INTERNATIONAL APPLICATION NO. PCT/IB98/02154	ATTORNEY'S DOCKET NUMBER 0769-0420-0X PCT

20. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS	PTO USE ONLY
☒ Search Report has been prepared by the EPO or JPO	**$840.00**		
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482)	**$670.00**		
☐ No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))	**$760.00**		
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO	**$970.00**		
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)	**$96.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =		**$840.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).		**$0.00**	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	19 - 20 =	0	x $18.00	**$0.00**	
Independent claims	1 - 3 =	0	x $78.00	**$0.00**	
Multiple Dependent Claims **(check if applicable)**.			☐	**$0.00**	
	TOTAL OF ABOVE CALCULATIONS =			**$840.00**	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable)**.			☐	**$0.00**	
	SUBTOTAL =			**$840.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).			+	**$0.00**	
	TOTAL NATIONAL FEE =			**$840.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable)**.			☐	**$0.00**	
	TOTAL FEES ENCLOSED =			**$840.00**	
				Amount to be: refunded	$
				charged	$

☒ A check in the amount of **$840.00** to cover the above fees is enclosed.

☐ Please charge my Deposit Account No. in the amount of to cover the above fees. A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **15-0030** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C.
Crystal Square Five, Fourth Floor
1755 Jefferson Davis Highway
Arlington, Virginia 22202
703-413-3000

WILLIAM E. BEAUMONT
REGISTRATION NUMBER 30,996

SIGNATURE

Norman F. Oblon
NAME

24,618
REGISTRATION NUMBER

May 18, 2000
DATE

DOCKET NO. 0769-0420-0X PCT

IN RE APPLICATION OF: Martha WARPEHOSKI, et al.

SERIAL NO.: NEW U.S. PCT APPLICATION (based on PCT/IB98/02154)

FILED: HEREWITH

FOR: ALPHA-HYDROXY, -AMINO AND -FLUORO DERIVATIVES OF BETA-SULPHONYL HYDROXAMIC ACIDS AS MATRIX METALLOPROTEINASES INHIBITORS

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

Sir:

Transmitted herewith is an amendment in the above-identified application.

☒ No additional fee is required.

☐ Small entity status of this application under 37 C.F.R. §1.9 and §1.27 has been established by a verified statement previously submitted.

☐ Small entity status of this application under 37 C.F.R. §1.9 and §1.27 has been established by a verified statement submitted herewith.

☒ Additional documents filed herewith: Declaration/Preliminary Amendment/Check for $840.00 PCT Transmittal Letter/PCT/IB/304/Request for Consideration/International Search Report International Preliminary Examination Report

The fee has been calculated as shown below.

	(Col. 1)		(Col. 2)	(Col. 3)	SMALL ENTITY		OTHER THAN A SMALL ENTITY	
	CLAIMS REMAINING AFTER		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	ADDITIONAL FEE	RATE	ADDITIONAL FEE
TOTAL	* 19	MINUS	** 20	= 0	X9 =	$	X18 =	$ .00
INDEP	* 1	MINUS	*** 3	= 0	X39 =	$	X78 =	$ .00
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM					+130=	$	+260=	$
					TOTAL	$	TOTAL	$ .00

___ A check in the amount of $____________ is attached.

XX Please charge any additional fees for the papers being filed herewith and for which no check is enclosed herewith, or credit any overpayment to deposit Account No. 15-0030. A duplicate copy of this sheet is enclosed.

XX If these papers are not considered timely filed by the Patent and Trademark Office, then a petition is hereby made under 37 C.F.R. §1.136, and any additional fees required under 37 C.F.R. §1.136 for any necessary extension of time may be charged to deposit Account No. 15-0030. A duplicate copy of this sheet is enclosed.

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Norman F. Oblon
Attorney of Record
Registration No.24,618
William E. Beaumont
Registration No. 30,996

Fourth Floor
1755 Jefferson Davis Highway
Arlington, Virginia 22202
(703) 413-3000

*If the entry in Column 2 is less than the entry in Column 1 write "0" in Column 3.
**If the "Highest Number Previously paid for" IN THIS SPACE is less than 20 write "20" in this space.
***If the "Highest Number Previously paid for" IN THIS SPACE is less than 3 write "3" in this space.

09/530965

422 Rec'd PCT/PTO 18 MAY 2000

0769-0420-0X PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF: :

MARTHA A. WARPEHOSKI ET AL : ATTN: APPLICATION DIVISION

SERIAL NO: NEW APPLICATION :
(Based on PCT/IB98/02154)

FILED: HEREWITH :

FOR: ALPHA-HYDROXY-AMINO AND : FLUORO DERIVATIVES OF BETA-SULPHONYL HYDROXAMIC ACIDS AS MATRIX METALLOTEINASES INHIBITORS

PRELIMINARY AMENDMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

Prior to examination on the merits, please amend the above-identified application as follows.

IN THE SPECIFICATION

Please amend the specification as follows:

Page 1, before line 1, delete the title of the invention in its entirety, and insert therefor:

- - ALPHA-HYDROXY, -AMINO AND -FLUORO DERIVATIVES OF BETA-SULPHONYL HYDROXAMIC ACIDS AS MATRIX METALLOPROTEINASES INHIBITORS - -.

IN THE CLAIMS

Please amend the claims as follows.

Claim 11, line 1, delete "of claim 1".

Claim 12, line 1, delete "of claim 1".

REMARKS

Claims 1-19 are active in this application.

The claims have been amended to remove multiple dependencies. No new matter is believed to have been added to this application by these amendments.

Applicants submit that the present application is ready for examination on the merits. Early notice to this effect is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Norman F. Oblon
Attorney of Record
Registration No. 24,618

James J. Kelly, Ph.D.
Registration No. 41,504

Crystal Square Five - Fourth Floor
1755 Jefferson Davis Highway
Arlington, VA 22202
(703) 413-3000
Fax #: (703)413-2220
JK/NFO/rac
I:\atty\JK\07690420.PR.wpd

WILLIAM E. BEAUMONT
REGISTRATION NUMBER 30,996

α-HYDROXY, -AMINO, AND HALO DERIVATIVES OF β-SULFONYL HYDROXAMIC ACIDS AS MATRIX METALLOPROTEINASES INHIBITORS

FIELD OF THE INVENTION

The present invention relates to novel α-hydroxy, amino, and halo derivatives of β-sulfonyl hydroxamic acids, to pharmaceutical compositions containing them, and to the method of using them. The compounds of the invention are inhibitors of matrix metalloproteinases involved in tissue degradation.

BACKGROUND OF THE INVENTION

Loss of connective tissue integrity occurs in many disease processes, including osteoarthritis, rheumatoid arthritis, septic arthritis, osteopenias such as osteoporosis, tumor metastasis (invasion and growth), periodontitis, gingivitis, corneal ulceration, dermal ulceration, gastric ulceration, inflammation, asthma and other diseases related to connective tissue degradation. Although there is a high incidence of these diseases in the developed world. there is no treatment that prevents the tissue damage that occurs. Considerable lines of scientific evidence indicate that uncontrolled connective matrix metalloproteinase (MMPs) activity is responsible for the damage, and as a consequence the inhibition of these enzymes has become the target for therapeutic intervention (see Matrisian, L. M., Bases, Vol. 14, pp 445-463 (1992); Emonard, H. et al., Cellular and Molecular Biology, Vol. 36, pp 131-153 (1990); Docherty, A. J. P. et al., Annals of the Rheumatic, Vol. 49, pp 469-479 (1990)).

Hydroxamic acid derivatives are a class of known therapeutically active MMPs inhibitors and there are numerous references in the art disclosing a variety of hydroxamic acid derivatives. For example, European Patent Publication No. 0,606,046 A1 discloses arylsulfonamido-substituted hydroxamic acids useful as matrix metalloproteinase inhibitors. International Publication Nos. WO 95/35275 and WO 95/35276 disclose sulfonamide hydroxamic acid and carboxylic acid derivatives useful as matrix metalloproteinases inhibitors. All these references relate to sulfonamide hydroxamic acids. The compounds of this invention are novel and distinct from all other sulfonamide hydroxamic acids in that the usual nitrogen atom is replaced by a carbon atom. The invention provides sulfonyl hydroxamic acid derivatives.

The compounds of the present invention inhibit various enzymes from the matrix metalloproteinase family, predominantly stromelysin and gelatinase, and hence are useful for the treatment of matrix metallo endoproteinase diseases such as osteoporosis, tumor metastasis (invasion and growth), periodontitis, gingivitis, corneal

ulceration, dermal ulceration, gastric ulceration, inflammation, asthma, and other diseases related to connective tissue degradation.

INFORMATION DISCLOSURE

The European Patent Application No. EP 0780 386 A1 discloses matrix metalloproteinases inhibitors useful in the treatment of mammals having disease states alleviated by the inhibition of such matrix metalloproteinases.

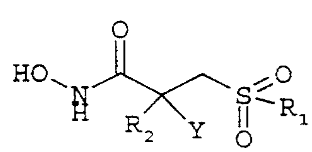
International Publication No. WO 97/24117 discloses substituted aryl, heteroaryl, arylmethyl or heteroarylmethyl hydroxamic acid compounds especially useful for inhibiting the production or physiological effects of TNF in the treatment of a patient suffering from a disease state associated with a physiologically detrimental excess of tumor necrosis factor (TNF).

International Patent Application No. PCT/US97/16348 discloses β-sulfonyl hydroxamic acids as matrix metalloproteinases inhibitors.

The compounds of the present invention are novel and distinct from the above hydroxamic acids in that they have a hydroxy, amino group or fluoro on the α-position and two hydrogen atoms at the β-position of the hydroxamate group.

SUMMARY OF THE INVENTION

The present invention provides novel compounds of formula I



I

or pharmaceutical acceptable salts thereof wherein:

R_1 is

a) C_{4-12} alkyl,

b) C_{4-12} alkenyl,

c) C_{4-12} alkynyl,

d) $-(CH_2)_h-C_{3-8}$ cycloalkyl,

e) $-(CH_2)_h$-aryl, or

f) $-(CH_2)_h$-het;

R_2 is

a) C_{1-12} alkyl,

b) C_{2-12} alkenyl,

c) C_{2-12} alkynyl,

d) $-(CH_2)_h-C_{3-8}$ cycloalkyl,

e) $-(CH_2)_h-C_{3-8}$ cycloalkenyl,

f) $-(CH_2)_h$-aryl,

g) $-(CH_2)_h$-het,

h) $-(CH_2)_h$-Q,

i) $-(CH_2)_i$-Q or $-(CH_2)_i-X-R_4$, optionally the $-(CH_2)_i-$ chain can be substituted with one or two C_{1-4} alkyl or phenyl, which in turn can be substituted with one to three halo or C_{1-4} alkyl, or

l) $-(CH_2)_hCHR_5R_6$;

R_3 is

a) H,

b) C_{3-6} cycloalkyl,

c) C_{1-4} alkyl, or

d) $-(CH_2)_h$-phenyl;

X is

a) -O-,

b) -S(=O)j-,

c) $-NR_7-$,

d) $-S(=O)_2NR_8-$, or

e) -C(=O)-;

R_4 is

a) H,

b) C_{1-8} alkyl,

c) $-(CH_2)_h$-phenyl, or

d) $-(CH_2)_h$-het;

R_5 is

a) C_{1-4} alkyl, or

b) $-C(=O)R_3$;

R_6 is

a) $-C(=O)R_3$, or

b) $-(CH_2)_hC(=O)R_3$;

R_7 is

a) H,

b) C_{1-4} alkyl,

c) $-(CH_2)_h$-phenyl,

d) $-C(=O)-R_3$,

e) $-S(=O)_2R_3$, or

f) $-C(=O)OR_3$;

R_8 is

a) C_{1-4} alkyl, or

b) $-(CH_2)_h$-phenyl;

Y is

a) -OH,

b) $-NR_9R_{10}$, or

c) fluoro;

R_9 and R_{10} are the same and different and are

a) H,

b) $-C(=O)-R_3$,

c) $-C(=O)-OR_3$, or

d) $-C(=O)-NHR_3$;

aryl is monocarbocyclic, or bicarbocyclic aromatic moiety;

het is 5- to 10-membered unsaturated monomonocyclic or bicyclic heterocyclic moiety having one to three atoms selected from the group consisting of oxygen, nitrogen, and sulfur;

Q is 5- to 10-membered saturated monocyclic or bicyclic heterocyclic moiety having one to two atoms selected from the group consisting of oxygen, nitrogen, and sulfur;

aryl, het, C_{1-12} alkyl, C_{1-4} alkyl C_{2-12} alkenyl, C_{2-12} alkynyl, $-C_{3-8}$ cycloalkyl, $-C_{3-8}$ cycloalkenyl, Q and phenyl being optionally substituted;

h is 0, 1, 2, 3, 4, 5, or 6; i is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; j is 0, 1, or 2; and with the following provisos: a) where R_2 is C_{1-6} alkyl, Y is other than $-NR_9R_{10}$, b) where h is 0, het and Q are attached to the α-position via carbon atom of heterocyclic moiety.

The compounds of the present invention inhibit various enzymes from the matrix metalloproteinase family, predominantly stromelysin and gelatinase, and hence are useful for the treatment of matrix metallo endoproteinase diseases.

DETAILED DESCRIPTION OF THE INVENTION

For the purpose of the present invention, the carbon content of various hydrocarbon containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety; i.e., the prefix C_{i-j} defines the number of carbon atoms present from the integer "i" to the integer "j", inclusive. Thus, C_{1-4} alkyl

refers to alkyl of one to four carbon atoms, inclusive, or methyl, ethyl, propyl, butyl and isomeric forms thereof.

As stated above, aryl, het, C_{1-4} alkyl , C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, Q and phenyl may be substituted as appropriate. Aryl is preferably substituted with C_{1-4} alkyl, C_{1-4} alkoxy, phenyl, O-phenyl, het, O-het, halo such as fluoro, chloro, bromo, OH, $-NO_2$, -CN, $-CF_3$, $-N(R_3)_2$ such as $-N(C_{1-4}$ alkyl$)_2$, $-SR_3$, $-SO_2(C_{1-4}$ alkoxy), $-(CH_2)_h$-het; $-C(=O)R_3$ or $-NHC(=O)R_3$; het is preferably substituted with C_{1-4} alkyl, pheny, phenoxy or halo; C_{1-12} alkyl is preferably substituted with one to three halo , CN, $-NO_2$ or $-CF_3$; $-N(R_3)_2$ such as $-N(C_{1-4}$ alkyl$)_2$, $-SR_3$ or -OH; C_{2-12} alkenyl, and C_{2-12} alkynyl are preferably substituted with one to three halo , CN, $-NO_2$ or $-CF_3$; C_{3-8} cycloalkyl and C_{3-8} cycloalkenyl are preferably substituted with one to three C_{1-4} alkyl, C_{1-4} alkoxy or halo; Q is preferably substituted with one to three C_{1-4} alkyl, C_{1-4} alkoxy, halo, oxo or phenyl; phenyl is preferably substituted with one to three C_{1-4} alkyl, C_{1-4} alkoxy, phenyl, phenoxy, het, halo, $-NO_2$ or -CN.

More preferably, in the meanings of R_1 , the optional substituents of $-(CH_2)_h$-aryl are selected from C_{1-4} alkyl,C_{1-4} alkoxy, phenyl, O-phenyl, het, O-het, halo, $-NO_2$, $-CF_3$, -CN, or $-N(C_{1-4}$ alkyl$)_2$; the optional substituents of $-(CH_2)_h$-het are selected from C_{1-4} alkyl, phenyl, phenoxy, het, or halo; in the meanings of R_2 , the optional substituents of C_{1-12} alkyl are one to three halo, -CN, $-NO_2$, $-CF_3$, $-N(R_3)_2$, $-SR_3$, or OH; the optional substituents of C_{2-12} alkenyl and C_{2-12} alkynyl are one to three halo, -CN, $-NO_2$, or $-CF_3$; the optional substituents of $-(CH_2)_h-C_{3-8}$ cycloalkyl and $-(CH_2)_h-C_{3-8}$ cycloalkenyl are one to three C_{1-4} alkyl, C_{1-4} alkoxy, or halo; the optional substituents of $-(CH_2)_h$-aryl are one to three C_{1-4} alkyl, C_{1-4} alkoxy, $-CF_3$ -OH, $-NO_2$, -CN, $-N(R_3)_2$, $-SR_3$, $-SO_2(C_{1-4}$ alkoxy), $-C(=O)R_3$, $-NHC(=O)R_3$, one to five halo; the optional substituents of $-(CH_2)_h$-het are one to two C_{1-4} alkyl, or halo; the optional substituents of $-(CH_2)_h$-Q are one to three C_{1-4} alkyl, C_{1-4} alkoxy, halo, oxo or phenyl; in the meanings of R_3 the optional substituents of $-(CH_2)_h$-phenyl are one to three C_{1-4} alkyl, C_{1-4} alkoxy, or halo; in the meanings of R_4 the optional substituents of $-(CH_2)_h$-phenyl are one to three C_{1-4} alkyl, C_{1-4} alkoxy, phenyl, phenoxy, het, halo, $-NO_2$, -CN -; in the meanings of R_7 and R_8 the optional substituents of $-(CH_2)_h$-phenyl are one to three C_{1-4} alkyl, C_{1-4} alkoxy, or halo. In the meanings of R_2, the preferred subsituent(s), when present, of the$-(CH_2)_i$- chain are one or two C_{1-4} alkyl, more preferably one or two methyl groups.

The terms "C_{1-4} alkyl", "C_{4-8} alkyl", "C_{1-12} alkyl", and "C_{1-18} alkyl" refer to an alkyl group having one to four, four to eight, one to twelve, or one to eighteen carbon atoms respectively such as: for example, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl,

octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl and their isomeric forms thereof, preferably an alkyl group of R_1 having four to eight carbon atoms, and an alkyl group of R_2 having one to eight carbon atoms.

The terms "C_{2-12} alkenyl" and "C_{4-8} alkenyl" refer to at least one double bond alkenyl group having two to twelve carbon atoms respectively such as; for example, ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl. heptdienyl, octenyl, octadienyl, octatrienyl, nonenyl, undecenyl, dodecenyl, and their isomeric forms thereof, preferably an alkenyl group of R_1 having four to eight carbon atoms, and an alkenyl group of R_2 having two to eight carbon atoms.

The term "C_{2-12} alkynyl" refers to at least one triple bond alkynyl group having two to twelve carbon atoms such as; for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, octadiynyl, octatriynyl, nonynyl, nonediynyl, and their isomeric forms thereof, preferably an alkynyl group of R_1 having four to eight carbon atoms, and an alkenyl group of R_2 having two to eight carbon atoms.

The term "C_{3-8} cycloalkyl" refers to a cycloalkyl having three to eight carbon atoms such as; for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and their isomeric forms thereof, preferably a cycloalkyl group having five or six carbon atoms.

The term "C_{3-8} cycloalkenyl" refers to a cycloalkenyl having three to six or three to eight carbon atoms such as; for example, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and their isomeric forms thereof, preferably a cycloalkyl group having five or six carbon atoms.

The terms "C_{1-4} alkoxy", "C_{1-6} alkoxy", and "C_{1-8} alkoxy" refer to an alkyl group having one to four, one to six, or one to eight carbon atoms respectively attached to an oxygen atom of hydroxyl group such as; for example, methoxy, ethoxy, propyloxy, butyloxy, pentyloxy, hexyloxy, heptyloxy, or octyloxy and their isomeric forms thereof.

The term "aryl" refers to monocarbocyclic or bicarbocyclic aromatic moiety such as; for example phenyl, naphthyl, and biphenyl. Each of these moieties may be substituted as appropriate. Aryl is preferably phenyl or phenyl substituted with C_{1-4} alkyl, C_{1-4} alkoxy, fluoro, chloro, bromo, $-NO_2$, $-CF_3$, $-N(C_{1-4}\text{ alkyl})_2$, $-C(=O)R_3$, or $-NHC(=O)R_3$.

The term "het" refers to a 5- to 10-membered unsaturated moncyclic or bicyclic heterocyclic moiety having one or more atoms selected from the group consisting of oxygen, nitrogen, and sulfur such as; for example, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 3-pyrazinyl, 2-quinolyl, 3-quinolyl, 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 2-quinazolinyl, 4-

quinazolinyl, 2-quinoxalinyl, 1-phthalazinyl, 2-imidazolyl, 4-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-isothiazole, 4-isothiazole, 5-isothiazole, 2-indolyl, 3-indolyl, 3-indazolyl, 2-benzoxazolyl, 2-benzothiazolyl, 2-benzimidazolyl, 2-benzofuranyl, 3-benzofuranyl, benzoisothiazole, benzoisoxazole, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 3-pyrrolyl, 3-isopyrrolyl, 4-isopyrrolyl, 5-isopyrrolyl, 1-indolyl, 1-indazolyl, 2-isoindolyl, 1-purinyl, 3-isothiazolyl, 4-isothiazolyl and 5-isothiazolyl, preferably pyridyl, quionlinyl, pyrrolyl, thienyl, thiazolyl, or indolyl. Each of these moieties may be substituted with one to two C_{1-4} alkyl, $-NO_2$, fluoro, chloro, or bromo as appropriate.

The term "Q" refers to a 5- to 10-membered saturated monocyclic or bicyclic heterocyclic moiety having one to two atoms selected from the group consisting of oxygen, nitrogen, and sulfur such as, for example, piperidinyl, 2-, 3-, or 4-piperidinyl, [1,4]piperazinyl, 2- or 3-morpholinyl, thiomorpholinyl, dioxolanyl, imidazolidinyl, [1,3]oxathiolanyl, [1,3]oxazolidinyl, pyrrolidinyl, butyrolactonyl, butyrolactamyl, succinimidyl, glutarimidyl, valerolactamyl, 2,5-dioxo-[1,4]-piperazinyl, pyrazolidinyl, 3-oxopyrazolidinyl, 2-oxo-imidazolidinyl, 2,4-dioxo-imidazolidinyl, 2-oxo-[1,3]-oxazolidinyl, 2,5-dioxo-[1,3]-oxazolidinyl, isoxazolidinyl, 3-oxo-isoxazolidinyl, [1,3]-thiazolidinyl, 2- or 4-oxo-[1,3]-thiazolidinyl, preferably butyrolactamyl, succinimidyl, glutarimidyl, valerolactamyl, 2,5-dioxo-[1,4]-piperazinyl, 3-oxopyrazolidinyl, 2-oxo-imidazolidinyl, 2,4-dioxo-imidazolidinyl, 2-oxo-[1,3]-oxazolidinyl, 2,5-dioxo-[1,3]-oxazolidinyl, 3-oxo-isoxazolidinyl, 2- or 4-oxo-[1,3]-thiazolidinyl.

The term halo refers to fluoro, chloro, bromo, or iodo, preferably fluoro, chloro, or bromo.

The compounds of the present invention can be converted to their salts, where appropriate, according to conventional methods.

The term "pharmaceutically acceptable salts" refers to acid addition salts useful for administering the compounds of this invention and include hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate, lactate, mesylate, maleate, malate, succinate, tartrate, citric acid, 2-hydroxyethyl sulfonate, fumarate and the like. These salts may be in hydrated form. Some of the compounds of this invention may form metal salts such as sodium, potassium, calcium and magnesium salts and these are embraced by the term "pharmaceutically acceptable salts".

The compounds of formula I of this invention contain a chiral center at the α-position of hydroxamic acids, as such there exist two enantiomers or a racemic mixture of both. This invention relates to both the enantiomers, as well as mixtures containing

both the isomers. In addition, depending on the substituents, additional chiral centers and other isomeric forms may be present in any of the R_2 groups, and this invention embraces all possible stereoisomers and geometric forms in this group.

R_1 is preferably n-butyl, isobutyl, 1-methylpropyl, tert-butyl, n-pentyl, 3-methybutyl, n-hexyl, n-heptyl, n-octyl, phenyl, 4-methylphenyl, 4-ethylphenyl, 4-tert-butylphenyl, 4-isopropylphenyl, 4-chlorophenyl, 4-bromophenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-n-butoxyphenyl, benzyl, 4-phenylbenzyl, 2-, 3-, or 4-fluorobenzyl, 2-, 3-, 4-chlorobenzyl, 2-, 3-, 4-bromobenzyl, 4-ethoxybenzyl, 4-phenylphenyl (i.e., biphenyl), 4-chlorobiphenyl, 4-phenoxyphenyl, 4-(pyrid-4-yl)phenyl, 4-(pyrid-4-yl)oxyphenyl, and 4-(benzamido)phenyl. More preferably R_1 is n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, phenyl, 4-methylphenyl, 4-ethylphenyl, 4-isopropylphenyl, 4-chlorophenyl, 4-bromophenyl, 4-fluorophenyl, 4-methoxyphenyl, 4-butoxyphenyl, benzyl, 4-fluorobenzyl, 4-chlorobenzyl, 4-bromobenzyl, 4-ethoxybenzyl, 4-phenylphenyl,4-n-butylphenyl, biphenyl, 4-chlorobiphenyl, 4-phenoxyphenyl, 4-(pyrid-4-yl)phenyl, and 4-(pyrid-4-yl)oxy-phenyl.

R_2 is preferably 1-cyano-1-phenyl methyl, 2-cyano ethyl, 2-phenylethyl, 2-bromo-2-phenylethyl, 2-bromoethyl, propyl, isopropyl, 3-chloropropyl, 3-bromopropyl, n-butyl, isobutyl, 3-methylbutyl, 1-methylpropyl, tert-butyl, n-pentyl, 3-methybutyl, n-hexyl, n-heptyl, n-octyl, n-hexadecyl, n-octadecyl, 2-propenyl, 2-propynyl, 3-butenyl, 4-pentenyl, 3-butenynyl, 4-pentenynyl, cyclopentyl, cyclohexyl, cyclohexylmethyl, 2-cyclohexylethyl, 4-cyclohexylbutyl, dimethylaminomethyl, dimethylaminoethyl, dimethylaminopropyl, diethylaminopropyl, phenylaminomethyl, phenyl, 4-methylphenyl, 4-chlorophenyl, 4-bromophenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 4-nitrophenyl, 4-ethoxyphenyl, benzyl, 4-methylbenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 4-ethoxybenzyl, 4-nitrobenzyl, methylcarbonyl, 1-methylcarbonylmethyl, 2-phenylcarbonylethyl, isopropylcarbonyl, methoxycarbonyl, ethoxycarbonyl, 1,1-ethoxycarbonylmethyl, 2,2-ethoxycarbonylethyl, 1,2-ethoxycarbonylethyl, 2-methoxycarbonylpropyl, 3-methoxycarbonyl-propyl, 1-ethoxycarbonylmethyl, 1-ethoxycarbonylethyl, phenylcarbonyl, phenylcarbonylmethyl, pyridylcarbonylmethyl, pyridylmethyl, pyridylethyl, quinolinylmethyl, pyrrolylmethyl, indolylmethyl, thienyl, thiazolyl, thienylmethyl, thienylethyl, piperidinylmethyl, piperazinylmethyl,4-(methanesulfonyl)-piperazinylmethyl, morpholinomethyl, morpholinoethyl, morpholinopropyl, thiomorpholinomethyl, thiomorpholinopropyl, 3-(4-methoxy-

benzenesulfonyl)-aminopropyl, 3-hydroxy, 3-amino, or 3-phenoxy-propyl, 2-phenylethyloxy, (1-methylhydantoin-3-yl)methyl, (1-ethylhydantoin-3-yl)methyl, (1-propylhydantoin-3-yl)methyl, (1-isopropylhydantoin-3-yl)methyl, (1-benzyl-hydantoin-3-yl)methyl, (1,5,5-trimethylhydantoin-3-yl)methyl, (1-butylhylhydantoin-3-yl)methyl, (1-butyl-5,5-dimethyl-hydantoin-3-yl)methyl, 2-(1-methylhydantoin-3-yl)methyl-2-methylethyl, methylthiomethyl, ethylthiomethyl, butylthiomethyl, phenylthiomethyl, (2-methoxy)phenylthiomethyl, benzylthiomethyl, (pyrid-2-yl)thiomethyl, (pyrid-2-yl)methylthiomethyl, (2-methyl-5-oxo-6-hydroxy-2,5-dihydro-1,2,4-triazin-3-yl)thiomethyl, (2-aminothiazol-5-yl)thiomethyl, (1-methyl-1H-imidazol-2-yl)thiomethyl, (1-methyl-1H-imidazol-2-yl)methylthiomethyl, (1-benzyl-1H-imidazol-2-yl)thiomethyl, (1-benzyl-1H-imidazol-2-yl)methylthiomethyl, (1-methyltetrazol-5-yl)thiomethyl, (tetrazolo-[1,5-b]pyridazin-6-yl)thiomethyl, (5-methylisoxazol-3-yl)thiomethyl, (5-methylisoxazol-3-yl)methylthiomethyl, 2-benzylthio-2-methylethyl, 2-(pyrid-2-yl)methylthio-2-methyl-ethyl, 2-(1-methyl-1H-imidazol-2-yl)methylthio-2-methylethyl, 2-(1-benzyl-1H-imidazol-2-yl)methylthio-2-methylethyl, 2-(5-methylisoxazol-3-yl)methylthio-2-methylethyl, (4-methoxybenzene-sulfonyl)methyl, (4-butoxybenzenesulfonyl) methyl, (4-chloro-benzenesulfonyl)methyl, (4-bromobenzenesulfonyl)methyl, (n-butylsulfonyl)methyl, (n-octylsulfonyl)methyl, 3-(4-methoxy-benzenesulfonyl)propyl, (4-methylbenzenesulfonyl) methyl, (benzenesulfonyl)methyl, (4-phenylbenzenesulfonyl)methyl, (4-n-butyl phenylsulfonyl) methyl, benzenecarbonylamino or cyclopentanecarbonylamino. More preferably R_2 is (4-methoxy-benzenesulfonyl)methyl, (4-fluorobenzenesulfonyl)methyl, (4-phenylbenzenesulfonyl)methyl, (4-n-butylphenylsulfonyl)methyl, benzenecarbonylamino, cyclopentanecarbonylamino, piperazinyl-methyl,4-(methanesulfonyl)piperazinylmethyl, morpholinomethyl, (1-methylhydantoin-3-yl)methyl, (1,5,5-trimethylhydantoin-3-yl)methyl, (1-butylhylhydantoin-3-yl)methyl, 2-(1-methyl-hydantoin-3-yl)methyl-2-methylethyl, phenylthiomethyl, (2-methoxy)phenylthiomethyl, benzylthiomethyl, (pyrid-2-yl)thiomethyl, (pyrid-2-yl)methylthiomethyl, (5-methylisoxazol-3-yl)thiomethyl, (5-methylisoxazol-3-yl)methylthiomethyl, 2-benzylthio-2-methylethyl, 2-(pyrid-2-yl)methylthio-2-methyl-ethyl, 2-(1-methyl-1H-imidazol-2-yl)methylthio-2-methylethyl, 2-(1-benzyl-1H-imidazol-2-yl)methylthio-2-methylethyl, and 2-(5-methylisoxazol-3-yl)methylthio-2-methylethyl.

Y is preferably a hydroxy group.

Examples of the compounds of this invention are as follows:

N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-phenylbenzenesulfonyl)-propionamide,

N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-fluorobenzenesulfonyl)-propionamide,

N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-n-butylbenzenesulfonyl)-propionamide,

N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-methoxybenzenesulfonyl)-propionamide,

N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(N-benzenecarbonylamino)-propionamide,

N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-[N-(cyclopentylcarbonyl)amino]-propionamide,

N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl) methyl]-3-(N-(4-methoxybenzenecarbonyl)amino)-propionamide,

N-Hydroxy-2-hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-(4-methoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-methoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-(4-butoxy-benzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-(4-butoxy-benzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-butoxy-benzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(methylthio)methyl-3-(4-butoxybenzenesulfonyl)-propionamide;

N-Hydroxy-2-hydroxy-2-(phenylthio)methyl-3-(4-butoxybenzenesulfonyl)-propionamide;

N-Hydroxy-2-hydroxy-2-(benzylthio)methyl-3-(4-butoxybenzenesulfonyl)-propionamide;

N-Hydroxy-2-hydroxy-2-(pyrid-2-yl)thiomethyl-3-(4-butoxybenzenesulfonyl)-propionamide;

N-Hydroxy-2-hydroxy-2-(2-methyl-5-oxo-6-hydroxy-2,5-dihydro-1,2,4-triazin-3-yl)thiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(2-aminothiazol-5-yl)thiomethyl-3-(4-butoxy-benzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(2-methyl-1,3,4-thiadiazol-5-yl)thiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methyl-1H-imidazol-2-yl)thiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methyltetrazol-5-yl)thiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(tetrazolo[1,5-b]pyridazin-6-yl)thiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(pyrid-2-yl)methylthiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methyl-1H-imidazol-2-yl)methylthiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-benzyl-1H-imidazol-2-yl)methylthiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(5-methylisoxazol-3-yl)methylthiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(2-benzylthio-2-methylethyl)-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-[2-(pyrid-2-yl)thio-2-methylethyl]-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-(4-chlorobiphenylsulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-(4-chlorobiphenylsulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-chlorobiphenylsulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(phenylthio)methyl-3-(4-chlorobiphenylsulfonyl)-propionamide;

N-Hydroxy-2-hydroxy-2-(benzylthio)methyl-3-(4-chlorobiphenylsulfonyl)-propionamide;

N-Hydroxy-2-hydroxy-2-(pyrid-2-yl)methylthiomethyl-3-(4-chlorobiphenylsulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(5-methylisoxazol-3-yl)methylthiomethyl-3-(4-chlorobiphenylsulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-[2-(1-methylhydantoin-3-yl)-2-methylethyl]-3-(4-chlorobiphenylsulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-[2-(pyrid-2-yl)thio-2-methylethyl]-3-(4-chlorobiphenylsulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-(4-phenoxy-benzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-(4-phenoxy-benzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-phenoxy-benzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-benzylhydantoin-3-yl)methyl-3-(4-phenoxy-benzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(phenylthio)methyl-3-(4-phenoxybenzenesulfonyl)-propionamide;

N-Hydroxy-2-hydroxy-2-(benzylthio)methyl-3-(4-phenoxybenzenesulfonyl)-propionamide;

N-Hydroxy-2-hydroxy-2-(pyrid-2-yl)methylthiomethyl-3-(4-phenoxybenzene-sulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methyl-1H-imidazol-2-yl)methylthiomethyl-3-(4-phenoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-[2-(1-methylhydantoin-3-yl)-2-methylethyl]-3-(4-phenoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-[2-(1-methyl-1H-imidazol-2-yl)thio-2-methylethyl]- (4-phenoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-[4-(pyrid-4-yl)-benzenesulfonyl]propionamide;

N-Hydroxy-2-hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-[4-(pyrid-4-yl)-benzenesulfonyl]propionamide;

N-Hydroxy-2-hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-[4-(pyrid-4-yl)benzenesulfonyl]propionamide;

N-Hydroxy-2-hydroxy-2-(phenylthio)methyl-3-[4-(pyrid-4-yl)benzenesulfonyl]-propionamide;

N-Hydroxy-2-hydroxy-2-(benzylthio)methyl-3-[4-(pyrid-4-yl)benzenesulfonyl]-propionamide;

N-Hydroxy-2-hydroxy-2-(2-benzylthio-2-methylethyl)-3-[4-(pyrid-4-yl)-benzenesulfonyl]-propionamide;

N-Hydroxy-2-hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-[4-(pyrid-4-yl)oxybenzenesulfonyl]propionamide or

N-Hydroxy-2-hydroxy-2-(benzylthio)methyl-3-[4-(pyrid-4-yl)oxybenzene-sulfonyl]propionamide.

The compounds of this invention can be prepared in accordance to the process discussed below.

In Scheme I, R_1 and R_2 are the groups as defined previously. Substituted malonate esters 2 are either obtained commercially, or can be readily prepared from structure 1 by methods well known to those skilled in the art. For example, reaction of an enolate of structure 1, generated by an appropriate base in an appropriate solvent, with an alkylating agent R_2-I (I is bromo, chloro, tosylate, mesylate, epoxides, etc.) provides the desired substituted malonate esters 2. See: Organic Synthesis, Vol. 1, p 250 (1954); Organic Synthesis, Vol. 3, p 495 (1955). Compound 2 is hydrolyzed to mono-acid compound 3 by reaction with one equivalent of an appropriate base such as alkali hydroxide in an appropriate solvent at a temperature ranging from 0° C to 30° C. In the presence of formaldehyde and piperidine in an appropriate solvent such as pyridine, ethanol, dioxane at refluxing temperatures, compound 3 is converted to acrylic esters 4. In many cases, acrylic esters 4 are commercially available. Acrylic esters 4 may be converted to glycidic esters 5 by oxidation with meta-chloroperoxybenzoic acid (MCPBA) in refluxing ethylene dichloride in the presence of a radical inhibitor such as 4,4'-thiobis-(6-t-butyl-3-methyl-phenol). See: J.C.S.Chem.Comm., pp 64-65 (1972). A thiol (H-SR_1) is added to the glycidic ester 5 at room temperature to afford sulfide esters 6 in the presence of a base such as sodium hydride in dry THF, or potassium carbonate in toluene, or a tertiary amine in chloroform. The resultant sulfides 6 are readily oxidized to sulfones 7 by an oxidizing agent such as MCPBA in an appropriate solvent such as methylene chloride, or using hydrogen peroxide in acetic acid as solvent. Alternatively, glycidic esters 5 may be converted to sulfones 7 directly by reaction with sodium sulfinate salts in solvents such as DMF or toluene. The esters can be hydrolyzed by procedures well known in the art such as using 6N HCl and refluxing for 10 to 20 hours or using iodotrimethylsilane in chloroform, or by saponification with aqueous alkali in alcoholic solvents at 0° C to room temperature, to afford free acids 8. Coupling of acids 8 with hydroxylamine hydrochloride to form hydroxamates 10 may be achieved by several routes well known to those skilled in the art. For example, acids 8 can be activated by chloroethylformate in dry THF or a similar compatible solvent, or by a carbodiimide condensing agent such as EDC, with or without HOBT, in DMF and methylene chloride. A tertiary amine is required in both situations. The subsequent reaction of activated 8 with hydroxylamine provides the desired hydroxamic acid derivatives. Alternatively, acids 8 may be condensed, using the same reagents as described above, or using two equivalents of EDC in aqueous THF, with benzyl-protected hydroxylamine hydrochloride, to produce the protected hydroxamates 9.

Compounds 9 are often easier to purify, and may readily be hydrogenolytically cleaved to the free hydroxamates 10 by a palladium catalyst in alcoholic solvents. Other protected hydroxylamines, such as tert-butyl hydroxylamine may also be used, and the free hydroxamic acid can be obtained by treating it with trifluoroacetic acid.

A second method of preparing the compounds of the invention particularly applicable to compounds of formula I wherein the R_2 group contains heteroatoms is to utilize commercially available bromomethyl acrylic acid esters such as 11, as shown in Scheme II. Treatment of 11 with thiols affords compounds 12. The reaction may be accomplished in dioxane, ethanol, toluene, or other appropriate solvent, at room temperature or reflux, with a base such as sodium bicarbonate or piperidine. See: Annelen, Vol.564, pp 73-78 (1949). Ester 11 may also be converted directly to the sulfone 13 by treatment with sodium sulfinate salts in DMF, toluene, methanol, or other appropriate solvent at room temperature or reflux, with or without sodium iodide as catalyst. See: Tetrahedron Lett., Vol.28, pp 813-816 (1987). Sulfides 12 or sulfones 13 can be oxidized to glycidic esters 14 by oxidation with a sufficient amount of MCPBA in refluxing ethylene dichloride in the presence of a radical inhibitor such as 4,4'-thiobis-(6-t-butyl-3-methyl-phenol), as referenced above. The glycidic esters 14 may be reacted with nucleophilic compounds W-H or alkaline salts thereof (wherein W is a group attached via a heteroatom such as oxygen, nitrogen, sulfur, or halogen) to afford the - hydroxy esters 7 (R_2 =CH_2-W). These reactions may be accomplished in methanol, DMF, toluene, or other appropriate solvents at room temperature or reflux. See: Tetrahedron, Vol. 51, pp 11841-11854 (1995) for an example of this reaction. Nucleophilic addition to glycidic esters may be facilitated by coordinating ions such as Mg^{2+} or other species such as titanium alkoxides. See: Tetrahedron Lett., Vol. 28, pp 4435-4436 (1987) and J. Org. Chem., Vol. 50, pp 1560-1563 (1985). Compounds 7 may be converted to hydroxamic acids 10 according to the methods described in Scheme I. Alternatively, bromomethyl acrylic acid esters 11 may be reacted first with nucleophiles W-H or alkaline salts thereof under the above-described conditions to afford acrylic esters 4, wherein R_2 is -CH_2W. Compounds 4 can be converted to hydroxamic acids 10, wherein R_2 is -CH_2W, according to the procedures described for Scheme I.

Scheme III illustrates the special case of Scheme II wherein glycidic ester 14 is reacted with a thiol or thiolate, as the nucleophile W-H or its alkaline salt, to afford the α-hydroxy esters 7 (R_2 = -CH_2-S-R4). The reaction may be accomplished in THF, toluene, or other appropriate solvent, with the thiol and an appropriate base such as sodium hydride or potassium carbonate, at room temperature or reflux. These esters may be oxidized to the bis-sulfone esters 15 with MCPBA in methylene chloride, or

hydrogen peroxide in acetic acid. Alternatively, the bis-sulfone esters 15 may be prepared directly from glycidic esters 14 by reaction with the sodium sulfinate salts in DMF, toluene, methanol, or other appropriate solvent at room temperature or reflux, with or without sodium iodide as catalyst. Hydrolysis of bis-sulfone esters 15 to the carboxylic acids 8 (R_2 = $-CH_2-S(O)_2-R_4$), and subsequent conversion to hydroxamic acids 10 (R_2 = $-CH_2-S(O)_2-R_4$), may be accomplished in accordance with the methods described in Scheme 1. In the special case wherein R_1 is the same as R_4, the resulting hydroxamic acids are achiral molecules.

Another variation of Scheme II is shown in Scheme IV, wherein glycidic ester 14 is reacted with a nitrile compound R_3CN in the presence of an acidic catalyst, preferably boron trifluoride etherate in methylene chloride, to afford the oxazoline esters 16. See: Recueil des Travaux Chimiques des Pays-Bas, Vol. 111, pp 69-74 (1992). The reaction is accomplished in several days at room temperature. The oxazoline esters 16 are hydrolyzed to the α-hydroxy esters 7 (R_2 = $-CH_2-NHCOR_3$) in the presence of acids, preferably oxalic acid in refluxing ethanol. Subsequent conversion of the esters 7 to the hydroxamic acids 10 (R_2 = $-CH_2-NHCOR_3$) is accomplished by the methods described in Scheme I.

Scheme V illustrates a method whereby compounds of this invention having a heterocyclic moiety may be prepared. Glycidic esters 14 may be reacted with t-butoxycarbonyl (Boc)-protected aminoacrylonitrile, for example, according to the methods of Scheme IV, to afford initially the oxazoline esters 17, and then the α-hydroxy esters 18 (R_2 = $-CH_2-NHCOCH_2NHBoc$). Deprotection of the Boc group with trifluoroacetic acid, followed by reaction of the amine with an acylating agent such as ethyl chloroformate in a solvent such as methylene chloride in the presence of a tertiary amine base such as triethylamine, and subsequent intramolecular acylation of the amide nitrogen may be utilized to afford compounds 19, containing, for example, a hydantoin ring. Conversion of compounds 19 to hydroxamic acids 20 may be accomplished by the methods described in Scheme I. By similar reactions well known in the art, and utilizing other readily available nitrile derivatives and acylating or alkylating agents, compounds 19 containing other nitrogen heterocycles can be prepared, and converted to compounds of this invention.

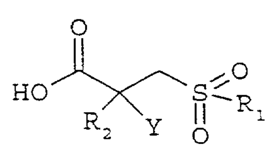
Scheme VI describes a method of preparing compounds of formula I, wherein Y= $-NH_2$ or $-NHR_9$, via the glycidic esters 5. Thus reaction of glycidic esters 5 with sodium azide in aqueous ethanol affords the azido alcohols 21. Refluxing the azido alcohols with triphenylphosphine in acetonitrile generates the aziridines 22. The aziridines undergo ring opening with thiol HSR_1 (followed by oxidation to the sulfone

with MCPBA) or with sulfinate salts directly to afford the α-amino esters 23. This reaction may be aided by using boron trifluoride etherate as a Lewis acid catalyst, in methylene chloride. See: J. Org. Chem., Vol. 60, p 790 (1995). Compounds 23 may be converted to the amino acids 24, and thence to hydroxamates 25 by the methods described in Scheme I. The amino group of compounds 22, 23, 24, or 25 may be protected by a Boc group or other amino-protecting group by methods well known to those skilled in the art.

The preparation of compounds of formula I wherein Y = F can be accomplished by the methods shown in Scheme VII. The α-hydroxy esters 7 may be converted to the α-fluoro esters 26 by use of diethylaminosulfur trifluoride (DAST) in a solvent such as methylene chloride at 0° C to room temperature. See: J. Org. Chem., Vol. 40, p 574 (1975). Compounds 26 may be converted to the α-fluoro hydroxamic acids 27 by the methods described in Scheme I.

The chemistry in Schemes I-VII proceeds through achiral or racemic intermediates and pure enantiomers of the final products may be obtained by resolution of intermediates 5-9, 14-19, 21-24, or 26 or final products 10, 20, 25, or 27 by chiral chromatography or by classical derivatization methods such as chiral salt formation of carboxylic acid intermediates such as 8 or 24.

The present invention also provides novel compounds of formula 8



8

or pharmaceutical acceptable salts thereof wherein R_1, R_2 and Y are as defined above. Examples of the compounds of formula 8 are as follows:

2-Hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-(4-butoxy-benzenesulfonyl)propionic acid;

2-Hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-butoxybenzenesulfonyl)propionic acid;

2-Hydroxy-2-(phenylthio)methyl-3-(4-butoxybenzene-sulfonyl)propionic acid;

2-Hydroxy-2-(benzylthio)methyl-3-(4-butoxybenzene-sulfonyl)propionic acid;

2-Hydroxy-2-(2-benzylthio-2-methylethyl)-3-(4-butoxy-benzenesulfonyl)propionic acid;

2-Hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-(4-chloro-biphenylsulfonyl)propionic acid;

2-Hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-(4-chloro-biphenylsulfonyl)propionic acid;

2-Hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-chlorobiphenylsulfonyl)propionic acid;

2-Hydroxy-2-(phenylthio)methyl-3-(4-chlorobiphenyl-sulfonyl)propionic acid;

2-Hydroxy-2-(benzylthio)methyl-3-(4-chlorobiphenyl-sulfonyl)propionic acid;

2-Hydroxy-2-(pyrid-2-yl)thiomethyl-3-(4-chlorobiphenyl-sulfonyl)propionic acid;

2-Hydroxy-2-(5-methylisoxazol-3-yl)methylthiomethyl-3-(4-chlorobiphenylsulfonyl)propionic acid;

2-Hydroxy-2-[2-(1-methylhydantoin-3-yl)-2-methylethyl]-3-(4-chlorobiphenylsulfonyl)propionic acid;

2-Hydroxy-2-(2-benzylthio-2-methylethyl)-3-(4-chloro-biphenylsulfonyl)propionic acid;

2-Hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-(4-phenoxy-benzenesulfonyl)propionic acid;

2-Hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-(4-phenoxy-benzenesulfonyl)propionic acid;

2-Hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-phenoxybenzenesulfonyl)propionic acid;

2-Hydroxy-2-(phenylthio)methyl-3-(4-phenoxybenzene-sulfonyl)propionic acid;

2-Hydroxy-2-(benzylthio)methyl-3-(4-phenoxybenzene-sulfonyl)propionic acid;

2-Hydroxy-2-[2-(1-methylhydantoin-3-yl)-2-methylethyl]-3-(4-phenoxybenzenesulfonyl)propionic acid;

2-Hydroxy-2-[2-(1-methyl-1H-imidazol-2-yl)thio-2-methyl-ethyl]- (4-phenoxybenzenesulfonyl)propionic acid;

2-Hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-[4-(pyrid-4-yl)benzenesulfonyl]propionic acid;

2-Hydroxy-2-(phenylthio)methyl-3-[4-(pyrid-4-yl)benzene-sulfonyl]propionic acid or

2-Hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-[4-(pyrid-4-yl)oxybenzenesulfonyl]propionic acid.

The pharmaceutical compositions of this invention may be prepared by combining the compounds of formula I of this invention with a solid or liquid pharmaceutically acceptable carrier, and optionally, with pharmaceutically acceptable

adjuvants and excipients employing standard and conventional techniques. Solid form compositions include powders, tablets, dispersible granules, capsules and suppositories. A solid carrier can be at least one substance which may also function as a diluent, flavoring agent, solubilizer, lubricant, suspending agent, binder, tablet disintegrating agent, and encapsulating agent. Inert solid carriers include magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, cellulosic materials, low melting wax, cocoa butter, and the like. Liquid form compositions include solutions, suspensions and emulsions. For example, there may be provided solutions of the compounds of this invention dissolved in water, water-propylene glycol, and water-polyethylene glycol systems, optionally containing conventional coloring agents, flavoring agents, stabilizers and thickening agents.

The pharmaceutical composition is provided by employing conventional techniques. Preferably the composition is in unit dosage form containing an effective amount of the active component, that is, the compounds of formula I according to this invention.

The quantity of active component, that is the compounds of formula I according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application method, the potency of the particular compound and the desired concentration. Generally, the quantity of active component will range between 0.5% to 90% by weight of the composition.

In therapeutic use for treating a patient, suffering from or susceptible to diseases involving connective tissue degradation, or inhibiting various enzymes from the matrix metalloproteinase family, including collagenase, stromelysin, and gelatinase, the compounds or pharmaceutical compositions thereof will be administered orally, parenterally and/or topically at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level of active component in the patient undergoing treatment which will be effective to inhibit such enzymes. Generally, an effective amount of the active compound will be in the range of about 0.1 to about 100 mg/kg. It is to be understood that the dosages may vary depending upon the requirements of the patient, the severity of connective tissue degradation being treated, and the particular compounds being used. Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired blood-level or the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the

particular situation. If desired, the daily dose may also be divided into multiple doses for administration, e.g., two to four times per day.

The compounds of the present invention inhibit various enzymes from the matrix metalloproteinase family, predominantly stromelysin and gelatinase, and hence are useful for the treatment of matrix metallo endoproteinase diseases such as osteoarthritis, rheumatoid arthritis, septic arthritis, osteopenias such as osteoporosis, tumor metastasis (invasion and growth), periodontitis, gingivitis, corneal ulceration, dermal ulceration, gastric ulceration, inflammation, asthma and other diseases related to connective tissue degradation. Such diseases and conditions are well known and readily diagnosed by physician of ordinary skill.

Pharmaceutical compositions for parenteral administration will generally contain a pharmaceutically acceptable amount of the compounds according to formula I as a soluble salt (acid addition salt or base salt) dissolved in a pharmaceutically acceptable liquid carrier such as; for example, water-for-injection and a suitably buffered isotonic solution having a pH of about 3.5-6. Suitable buffering agents include; for example, trisodium orthophosphate, sodium bicarbonate, sodium citrate, N-methylglucamine, L(+)-lysine and L(+)-arginine, to name a few. The compounds according to formula I generally will be dissolved in the carrier in an amount sufficient to provide a pharmaceutically acceptable injectable concentration in the range of about 1 mg/ml to about 400 mg/ml. The resulting liquid pharmaceutical composition will be administered so as to obtain the above-mentioned inhibitory effective amount of dosage. The compounds of formula I according to this invention are advantageously administered orally in solid and liquid dosage forms.

The compounds and their preparations of the present invention will be better understood in connection with the following examples, which are intended as an illustration of and not a limitation upon the scope of the invention.

EXAMPLE 1 Preparation of N-hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl) methyl]-3-(4-phenylbenzenesulfonyl)-propionamide.

Step 1 Preparation of 2-[(4-methoxybenzenethio)methyl]-acrylic acid, ethyl ester.

To a mixture of ethyl bromomethylacrylate (1.6 g, 8.3 mmol) and 1.0 mL (8.1 mmol) of 4-methoxythiophenol in ethanol, cooled in an ice-water bath, is added, dropwise and with stirring, 8 mL of a 1 M aqueous solution of sodium bicarbonate. The reaction mixture is allowed to warm to ambient temperature, and stirred for 6 hours. The mixture is then concentrated, taken up in ethyl acetate, and washed twice with aqueous 10% hydrochloric acid and once with brine. It is dried over sodium sulfate and evaporated in

vacuo to a pale yellow oil. Chromatography on silica gel, eluting with methylene chloride, affords the title compound as a colorless oil.

^1H NMR ($CDCl_3$) δ 7.33, 6.82, 6.07, 5.32, 4.23, 3.78, 3.63, 1.31.

Step 2 Preparation of 2-(4-methoxybenzenesulfonyl)methyl-oxiranecarboxylic acid, ethyl ester.

To 2[(4-methoxybenzenesulfonyl)methyl]-acrylic acid, ethyl ester (38.4 g, 0.152 mol) in 200 mL of ethylene dichloride is added a small amount of the radical inhibitor 4,4'-thiobis-(6-t-butyl-3-methylphenol) [Ref: J.C.S. Chem. Commun., 1972, pp 64-65]. Technical grade m-chloroperoxybenzoic acid (MCPBA, 154 g) is added portionwise over about 45 minutes. The reaction becomes a heavy white slurry. Additional ethylene dichloride (150 mL) is introduced to facilitate stirring. The reaction is refluxed overnight, then cooled and concentrated under reduced pressure. The residue is mixed with ethyl acetate (250 mL) and aqueous sodium sulfite. Solid potassium bicarbonate is then slowly added. The phases are separated , and the aqueous phase is extracted with additional ethyl acetate (100 mL). The combined organic phases are washed with several portions of aqueous potassium bicarbonate, then saturated brine, and finally dried over magnesium sulfate. Filtration and evaporation provides the crude product as a pale yellow oil. Chromatography on silica gel, eluting with a gradient of 40% to 60% ethyl acetate in hexanes, affords the title compound. m.p. 77-79 °C;

^1H NMR (DMSO-d_6) δ 7.78, 7.16, 4.11, 4.04, 3.85, 3.73, 2.95, 1.16.

^{13}C NMR (DMSO-d_6) δ 168.4, 164.3, 132.3, 131.0, 115.3, 62.5, 58.5, 56.6, 53.2, 51.6, 14.6.

Step 3 Preparation of 2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-phenylbenzenethio)-propionic acid, ethyl ester.

Sodium hydride (0.212 g, 60% in oil) is placed in a flask and washed with hexane. The hexane is decanted. Biphenyl mercaptan (0.82 g, 5.3 mmol) is added as a solution in dry tetrahydrofuran (25 mL). There is foaming, and a heterogeneous mixture results. The reaction is stirred for 5 minutes at ambient temperature, and then a solution of 2-(4-methoxybenzenesulfonyl)methyl-oxiranecarboxylic acid, ethyl ester (1.46 6, 4.9 mmol) in 25 mL of dry tetrahydrofuran is added. The mixture, which turns yellow, is stirred overnight at ambient temperature. The reaction is quenched with 1 N HCl and tetrahydrofuran is removed under reduced pressure. The product is extracted with ethyl acetate. The organic phase is dried over magnesium sulfate, filtered, concentrated, and chromatographed on silica gel to afford the title compound as a white solid.

^1H NMR ($CDCl_3$) δ 7.81, 7.6-7.35, 6.98, 4.11, 3.98, 3.87, 3.68, 3.28, 1.21.

Step 4 Preparation of 2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-phenylbenzenesulfonyl)-propionic acid, ethyl ester.

To a solution of 2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-phenylbenzenethio)-propionic acid, ethyl ester (0.99 g, 2 mmol) in 100 mL of methylene chloride is added solid MCPBA (1.3 g, 68% by weight). The reaction mixture is stirred overnight at ambient temperature. Methylene chloride is removed under reduced pressure, and the residue is partitioned between ethyl acetate and aqueous sodium sulfite. The organic phase is washed with several portions of aqueous potassium bicarbonate to remove m-chlorobenzoic acid. It is then washed with brine, dried over magnesium sulfate, filtered, and concentrated to afford the title compound as a white solid.

^1H NMR ($CDCl_3$) δ 7.92, 7.80-7.72, 7.6, 7.47, 6.97, 4.29, 3.97, 3.86-3.58, 1.36.

Step 5 Preparation of 2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-phenylbenzenesulfonyl)-propionic acid.

To a solution of 2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-phenylbenzenesulfonyl)-propionic acid, ethyl ester (0.70 g, 1.3 mmol) in 25 mL of methanol is added sodium hydroxide (25 mmol in 10 mL of water). The reaction mixture is stirred at ambient temperature for 1 hour, and then quenched by the addition of 25 mL of 1 N HCl. Methanol is removed under reduced pressure, and the product is extracted with several portions of ethyl acetate. The organic phase is washed with brine, dried over magnesium sulfate, filtered, and concentrated to afford the title compound as a white solid.

^1H NMR ($CDCl_3$) δ 7.95, 7.82-7.72, 7.61-7.46, 6.98, 3.86, 3.86-3.70.

Step 6 Preparation of N-benzyloxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl) methyl]-3-(4-phenylbenzenesulfonyl)-propionamide.

To 2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-phenylbenzenesulfonyl)-propionic acid (0.6 g, 1.2 mmol) in 50 mL of methylene chloride is added 1-hydroxybenzotriazole monohydrate (0.185 g, 1.36 mmol), O-benzylhydroxylamine hydrochloride (0.218 g, 1.36 mmol), diisopropylethylamine (0.177 g, 1.36 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 0.262 g, 1.36 mmol), in that order. The clear, colorless solution is stirred overnight at ambient temperature. Methylene chloride is removed under reduced pressure and the residue is partitioned between ethyl acetate and water. The organic phase is washed with several portions of 1 N HCl and then with aqueous potassium bicarbonate. It is dried over magnesium sulfate, filtered, concentrated, and chromatographed on silica gel. Elution with 1:1 ethyl acetate:hexanes affords the title compound as a white solid.

^1H NMR ($CDCl_3$) δ 7.95, 7.83-7.74, 7.5-7.25, 7.01, 4.99, 3.88, 4.0-3.6.

Step 7 Preparation of N-hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl) methyl]-3-(4-phenylbenzenesulfonyl)-propionamide.

A mixture of N-benzyloxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-phenylbenzenesulfonyl)-propionamide (0.152 g), 10% palladium on carbon, and 50 mL of absolute ethanol is placed under 20 psi of hydrogen, and agitated overnight at ambient temperature. The mixture is filtered through a Celite pad, rinsing with ethanol and with ethyl acetate. Concentration of the filtrate affords the title compound.

m.p. 72-76 ^{o}C (softening), 120-125 ^{o}C (decomposition with bubbling);

^{1}H NMR (DMSO-d_6) δ 7.9-7.6, 7.55-7.40, 7.1-7.0, 3.82, 3.9-3.7.

Step 8 Racemic N-hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-phenylbenzenesulfonyl)-propionamide is resolved by chiral chromatography to yield enantiomer A and enantiomer B.

Chiral chromatography is performed on a preparative Chiralpak AD column 5.0 x 50 cm, eluting with methanol at 70 mL/min. The two samples resulting from this chromatography are separately dissolved in methanol, stirred with activated charcoal, filtered through celite and evaporated to dryness to yield purified Enantiomer A and Enantiomer B.

EXAMPLE 2 Preparation of N-hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl) methyl]-3-(4-fluorobenzenesulfonyl)-propionamide.

Following the general procedure outlined in EXAMPLE 1 (steps 1 to 7) and making non-critical variations, but starting with p-fluorophenyl mercaptan in step 3, in place of biphenyl mercaptan, the title compound is obtained.

m.p. 85-90 ^{o}C (softening), 110-115 ^{o}C (decomposition with bubbling);

^{1}H NMR (DMSO-d_6) δ 10.6, 8.86, 7.92-7.87, 7.75-7.72, 7.46-7.40, 7.11-7.08, 5.64, 3.85-3.69.

EXAMPLE 3 Preparation of N-hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl) methyl]-3-(4-n-butylbenzenesulfonyl)-propionamide.

Following the general procedure outlined in EXAMPLE 1 (steps 1 to 7) and making non-critical variations, but starting with p-n-butylphenyl mercaptan in step 3, in place of biphenyl mercaptan, the title compound is obtained.

m.p. 63-68 ^{o}C (softening), 150-160 ^{o}C (decomposition with bubbling);

^{1}H NMR (DMSO-d_6) δ 10.6, 7.76-7.71, 7.43-7.40, 7.11-7.08, 5.6, 3.75-3.72, 2.70-2.65, 1.60-1.55, 1.35-1.27, 0.93-0.88.

EXAMPLE 4 Preparation of N-hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl) methyl]-3-(4-methoxybenzenesulfonyl)-propionamide.

Following the general procedure outlined in EXAMPLE 1 (steps 1 to 7) and making non-critical variations, but starting with p-methoxyphenyl mercaptan in step 3, in place of biphenyl mercaptan, the title compound is obtained as a white solid.
m.p. 75-80 °C (softening), 150-165 °C (decomposition with bubbling);
^{1}H NMR (DMSO-d_6) δ 10.55, 8.83, 7.71, 7.08, 5.53, 3.83, 3.69;
^{13}C NMR (DMSO-d_6) δ 166.6, 163.5, 133.1, 130.7, 114.7, 73.5, 62.0, 56.2;
IR (mull) cm^{-1} 3417, 3342, 3316, 3102, 3077, 1682, 1597, 1581, 1520, 1498, 1324, 1295, 1271, 1257, 1150, 1089, 1074;
Calculated for $C_{18}H_{21}NO_9S_2$: C, 47.05; H, 4.61; N, 3.05; Found: C, 47.01; H, 4.56; N, 3.07.

EXAMPLE 5 Preparation of N-hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl) methyl]-3-(N-benzenecarbonylamino)-propionamide.

Step 1 Preparation of 2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(N-benzenecarbonylamino)-propionic acid, ethyl ester.

2-(4-Methoxybenzenesulfonyl)methyl-oxiranecarboxylic acid, ethyl ester (from EXAMPLE 1, Step 2, 0.3 g, 1 mmol), boron trifluoride etherate (0.495 mL, 4.0 mmol), and benzonitrile (0.36 mL, 4.0 mmol) are dissolved in 40 mL of methylene chloride. The reaction mixture is stirred at ambient temperature under a nitrogen atmosphere for three days, with the addition two times of 0.50 mL of boron trifluoride etherate. The solvent is removed under reduced pressure. The residue is dissolved in ethyl acetate and washed with saturated sodium bicarbonate and with brine, and dried over magnesium sulfate. The crude product is dissolved in 40 mL of absolute ethanol. Oxalic acid (0.30 g, 3.3 mmol) is added, and the solution is heated to 65 °C for 19 hours. The solvent is removed under reduced pressure. The oily residue is dissolved in ethyl acetate and washed with saturated sodium bicarbonate and with brine, and dried over magnesium sulfate. Chromatography on silica gel, eluting with 1:1 ethyl acetate:hexanes affords the title compound as a white solid.
^{1}H NMR ($CDCl_3$) δ 7.82-7.71, 7.55-7.41, 7.02-6.99, 6.57, 4.29-4.17, 3.88, 3.85-3.72, 3.60-3.56, 1.32-1.28;
MS (ES+) 422.1 (M+H), (ES-) 420.1 (M-H).

Step 2 Preparation of 2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(N-benzenecarbonylamino)-propionic acid.

A solution of 2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(N-benzenecarbonylamino)-propionic acid, ethyl ester (0.27 g) in 4 mL of methanol is stirred with 1 mL of 1 N sodium hydroxide for 3 hours. The reaction mixture is acidified with 1 N HCl and the solvent is removed under reduced pressure. The residue is triturated twice

with warm ethyl acetate. The ethyl acetate is removed, affording the title compound as a white solid.

^1H NMR (MeOD) δ 7.86-7.76, 7.54-7.39, 7.06-7.03, 3.91-3.85, 3.77-3.62;

MS (ES+) 394.1 (M+H), (ES-) 392.1 (M-H).

Step 3 Preparation of N-hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl) methyl]-3-(N-benzenecarbonylamino)-propionamide.

2-Hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(N-benzenecarbonylamino)-propionic acid (0.25 g, 0.63 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.24 g, 1.26 mmol), hydroxylamine hydrochloride (0.066 g, 0.95 mmol), and 5 mL of 1-methyl-2-pyrrolidinone are stirred under a nitrogen atmosphere at ambient temperature for 4 hours. Diethyl ether (100 mL) is added, and the mixture is stirred overnight. The ether is decanted from the oily residue. The oil is washed twice more with ether and then chromatographed on silica gel, eluting with 20% hexane and 4% acetic acid in ethyl acetate. The title compound is obtained as a white powder.

^1H NMR (MeOD) δ 7.87-7.79, 7.55-7.45, 7.09-7.06, 3.88, 3.84-3.55;

MS (ES-) 406.9 (M-H);

HRMS (EI) calcd for $C_{18}H_{20}N_2O_7S + H_1$ 409.1069, found 409.1076.

EXAMPLE 6 Preparation of N-hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl) methyl]-3-[N-(cyclopentylcarbonyl)amino]-propionamide.

Following the general procedure outlined in EXAMPLE 5 (steps 1 to 3) and making non-critical variations, but starting with cyclopantanecarbonitrile in step 1, in place of benzonitrile, the title compound is obtained as a white solid.

^1H NMR (MeOD) δ 7.86-7.83, 7.09-7.06, 3.88, 3.81-3.76, 3.54-3.39,2.71-2.58,2.03-1.67;

MS (ES+) 401.1 (M+H), (ES-) 399.1 (M-H).

HRMS (EI) calcd for $C_{17}H_{24}N_2O_7S + H_1$ 401.1382, found 401.1378.

EXAMPLE 7 Preparation of N-hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl) methyl]-3-(N-(4-methoxybenzenecarbonyl)amino)-propionamide.

Step 1 Preparation of 2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(N-(4-methoxybenzenecarbonyl)amino)-propionic acid.

Following the general procedure outlined in EXAMPLE 5 (steps 1 and 2) and making non-critical variations, but starting with 4-methoxybenzonitrile in step 1, in place of benzonitrile, the title compound is obtained as a white solid after lyophilization from water.

^1H NMR (MeOD) δ 7.86-7.83, 7.77-7.74, 7.07-7.06, 6.97-6.94,3.89-3.87, 3.83, 3.72-3.61;

MS (ES+) 423.9 (M+H), (ES-) 421.9 (M-H).

Step 2 Preparation of N-hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl) methyl]-3-(N-(4-methoxybenzenecarbonyl)amino)-propionamide.

2-Hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(N-(4-methoxybenzenecarbonyl)amino)-propionic acid (100 mg, 0.24 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (68 mg, 0.35 mmol), O-tert-butylhydroxylamine hydrochloride (118 mg, 0.944 mmol), and 4-methylmorpholine (131 mg, 0.354 mmol) are dissolved in 20 mL of methylene chloride. The reaction mixture is stirred under nitrogen for 6 hours. The solvent is removed under reduced pressure, and the residue is dissolved in ethyl acetate. The organic layer is washed with 1N sodium hydrogen sulfate, 5% sodium bicarbonate, and saturated brine and dried over magnesium sulfate. The solvent is removed to yield 71 mg of white solid which is recrystallized from methanol. The tert-butyl protecting group is removed by treatment with 50% trifluoroacetic acid in methylene chloride for 24 hours. The solvents are removed, and the crude product is purified by reverse phase chromatography on a C18 Vydac column using a water/acetonitrile elution system to yield the title compound as a white solid.

^1H NMR (MeOD) δ 7.87-7.84, 7.80-7.77, 7.09-7.06, 6.99-6.96, 3.88, 3.84, 3.70-3.59;

MS (ES+) 438.9 (M+H), (ES-) 436.8 (M-H);

HRMS (EI) calcd for $C_{19}H_{22}N_2O_8S + H_1$ 439.1175, found 439.1195.

EXAMPLE 8 Biological Activity Test

Inhibitory activity is evaluated in one or more of the MMP enzymes (stromelysin, gelatinase, and collagenase) in vitro using particle concentration fluorescence assay. An inhibitor binds to MMP enzymes which prevents the degradation of a substrate by stromelysin, gelatinase, or collagenase. The substrate has attached to it a fluorescein and a biotin moiety. The intact substrate then binds to an avidin-coated particle via the biotin moiety. Once the particle is washed and dried, a fluorescent signal is generated since the fluorescent group is attached to the particle. Without an inhibitor present, the substrate is degraded by MMP enzymes and the fluorescein group is removed, therefore, no fluorescent signal can be detected. Testing compounds are dissolved in DMSO to the desired concentration, then the solutions are diluted to 1:5 with MMP buffer (50 mM Tris-HCl, pH 7.5; 150 mM NaCl; 0.02% NaN_3). Serial two-fold dilutions of each

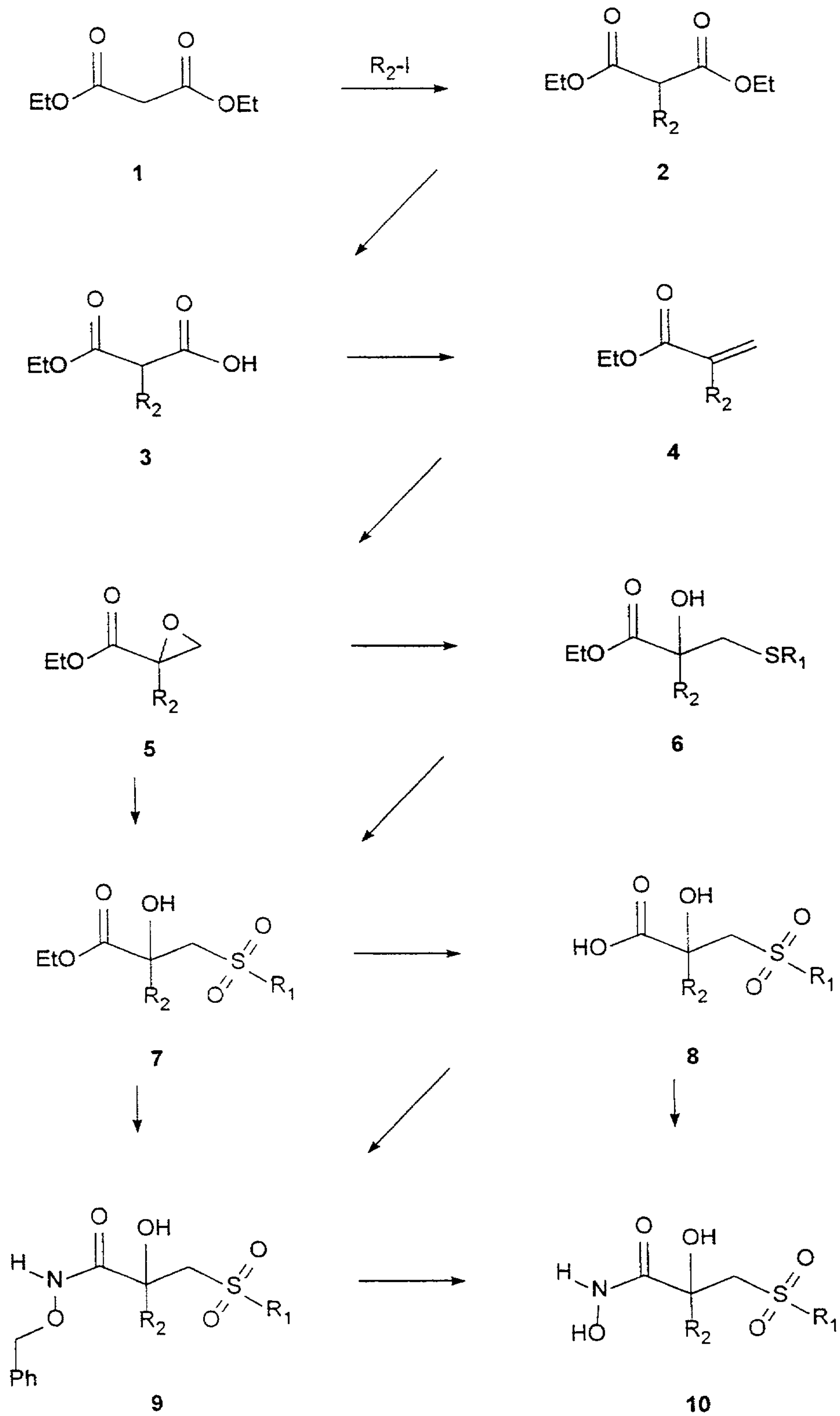
compound are prepared. A concentrated, activated enzyme solution is transferred into each plate of the testing compounds, and the mixture is incubated at room temperature for 15 minutes. Thawed MMP substrate is then added into all plates, and the plates are incubated in the dark for 1-3 hours at room temperature. At this point, the substrate mixture is mixed with 0.1% avidin-coated polystyrene particles. After 15 minutes, the fluorescence values are measured following filtration and washing of the beads. Ki values are then calculated. Inhibitory data for the compounds of this invention are shown in TABLE 1. Compounds with lower Ki values are expected to be more effective as MMP inhibitors. It is expected that a compound with a Ki less than 15 μM against stromelysin will display therapeutic effects in connective tissue disorders.

TABLE 1

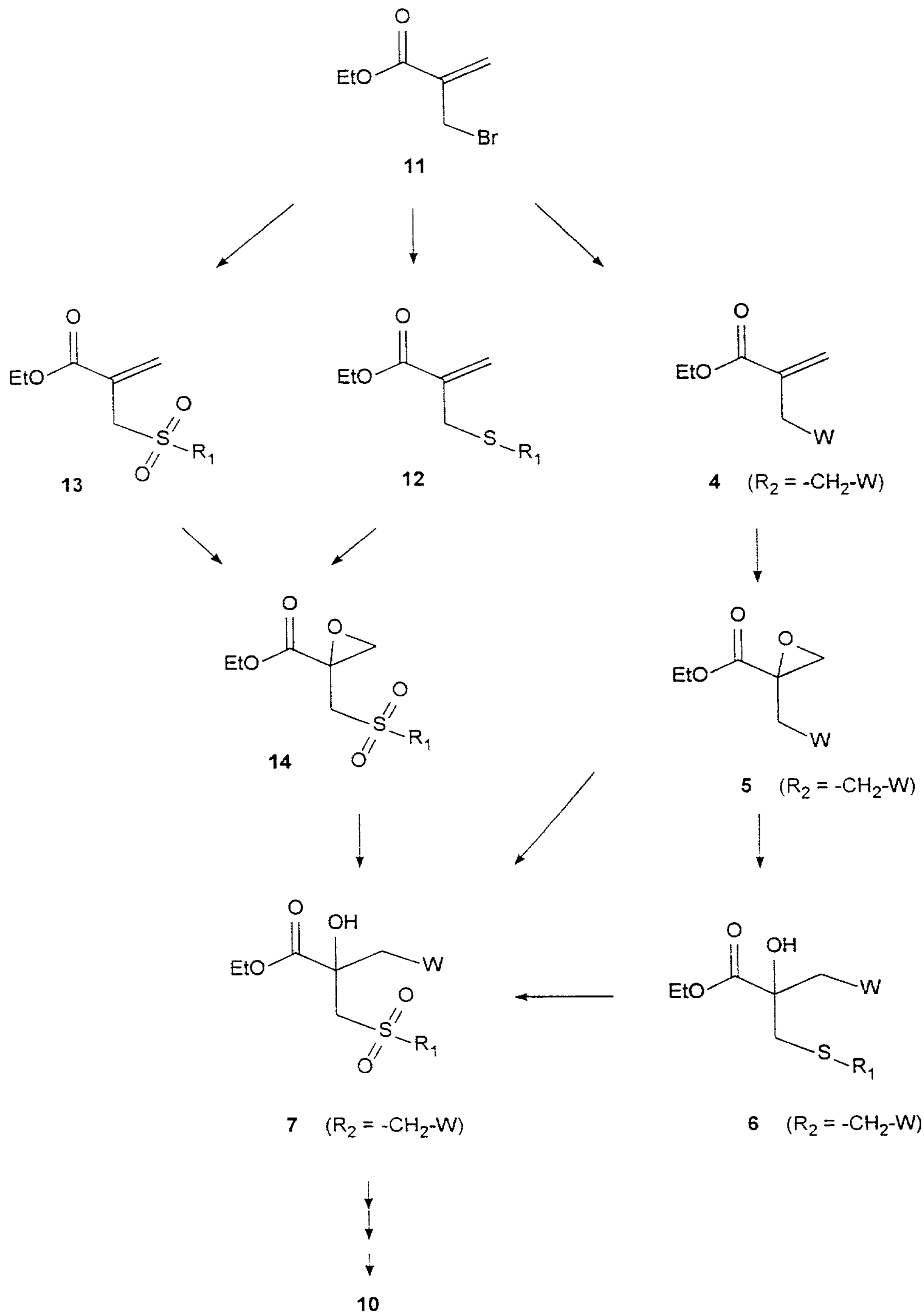
MMP Inhibition Constants (Ki, μM) of the Compounds of the Invention

Example No.	Stromelysin Ki (μM)	Gelatinase Ki (μM)
1	0.074	0.0019
1, Enantiomer A	0.021	0.0085
1, Enantiomer B	0.080	0.00034
2	0.18	0.031
3	0.046	0.013
4	0.039	0.0075
5	0.24	0.023
6	0.35	0.070
7	0.28	0.017

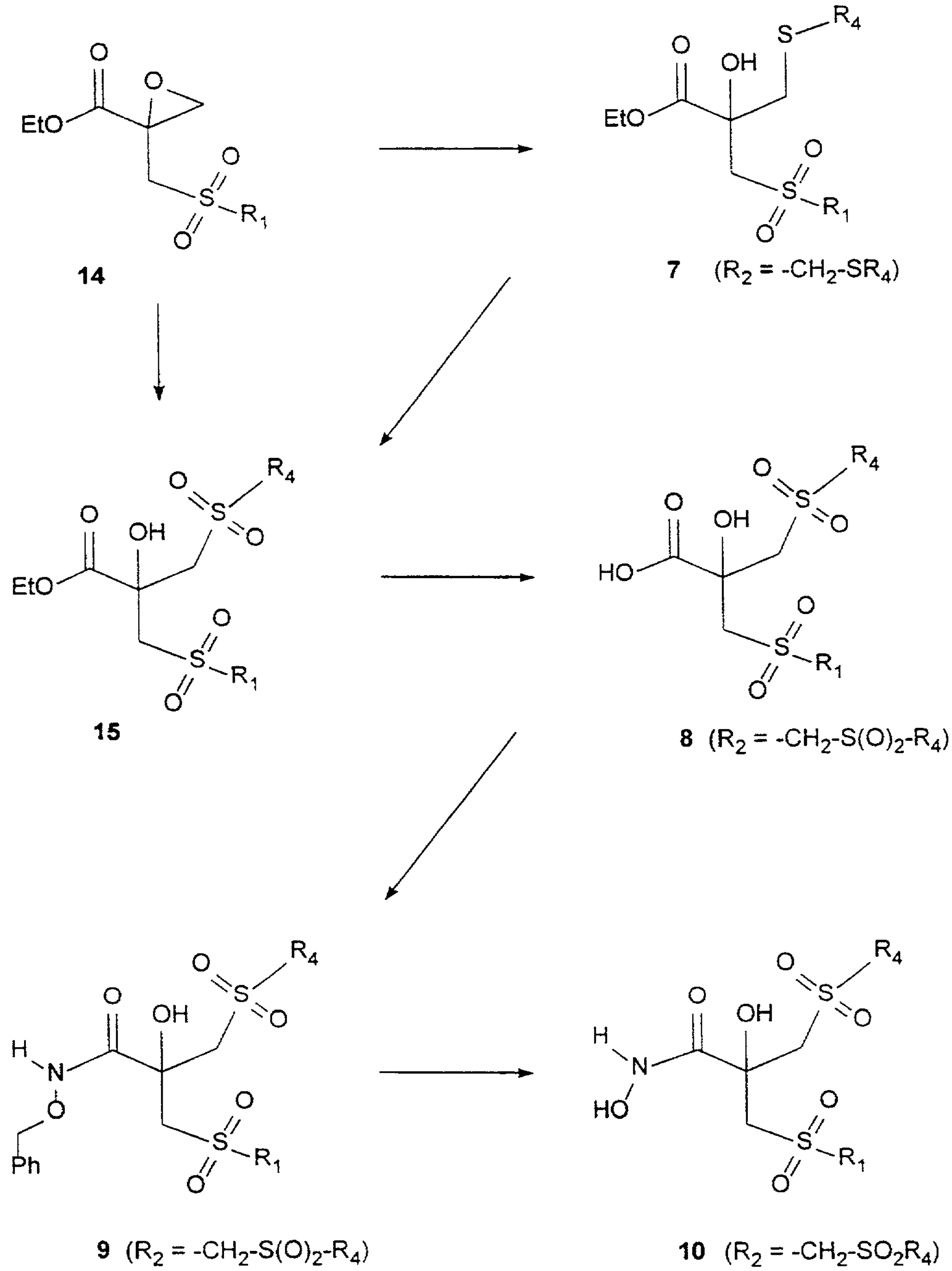
SCHEME I



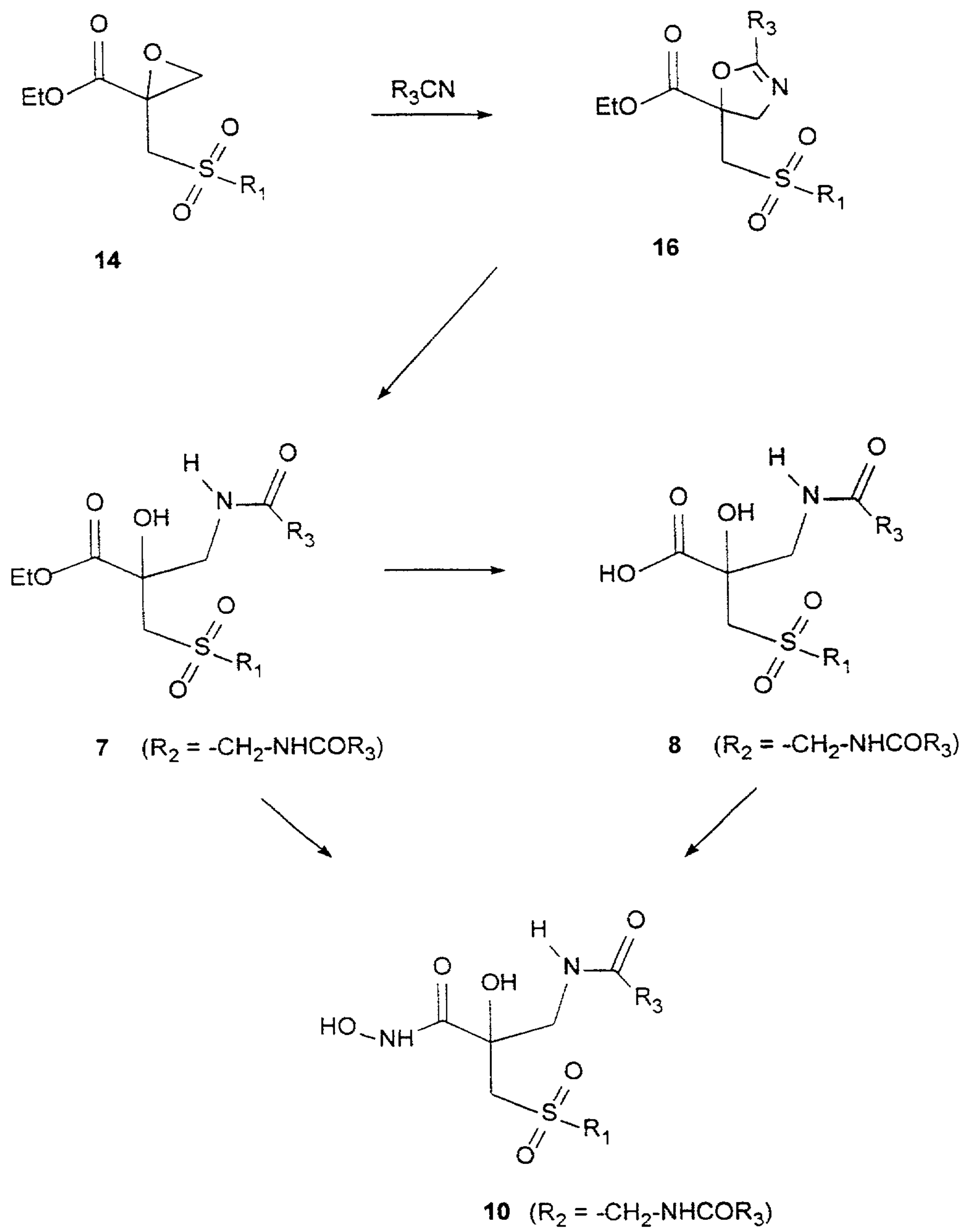
SCHEME II



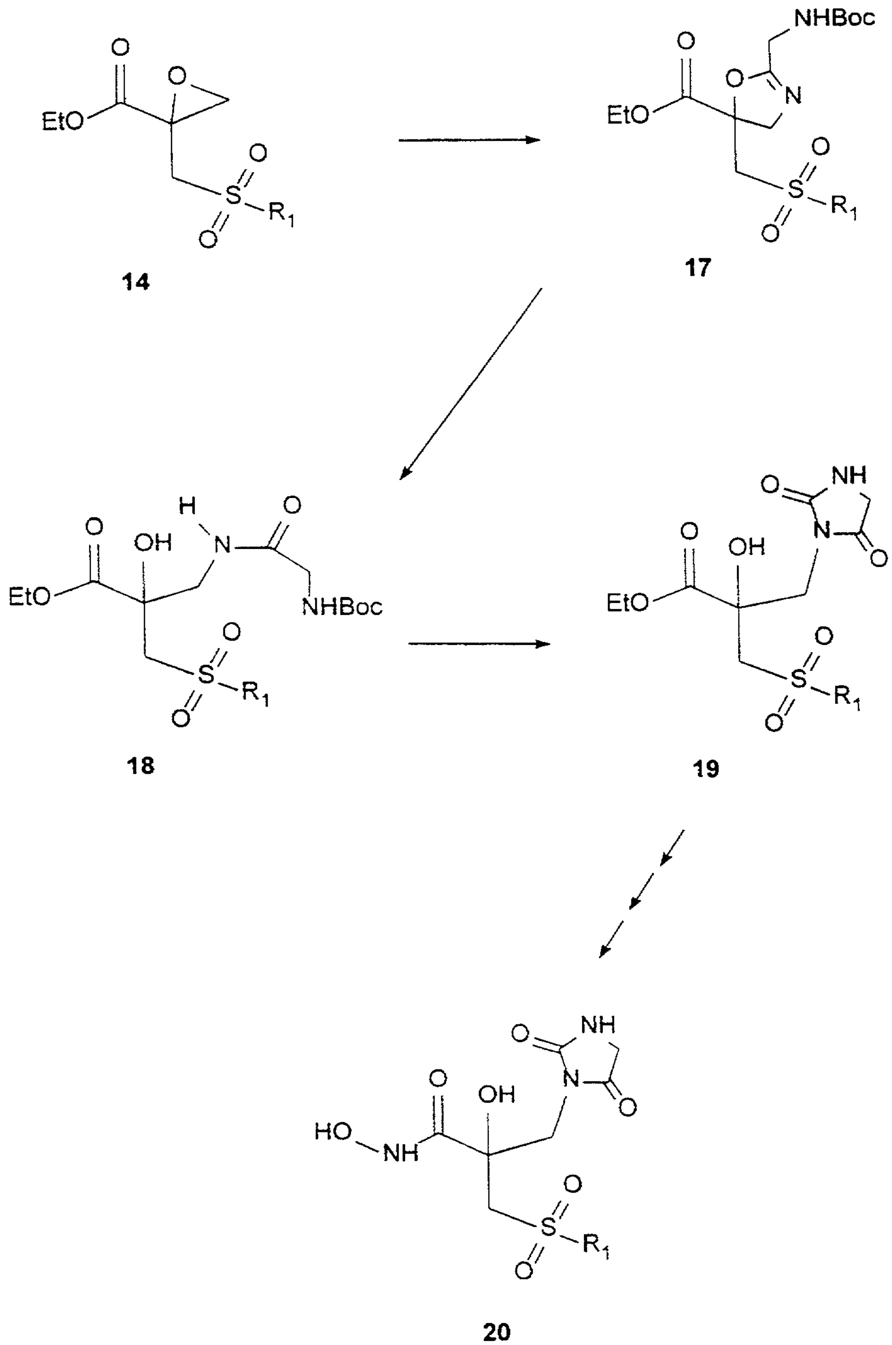
SCHEME III



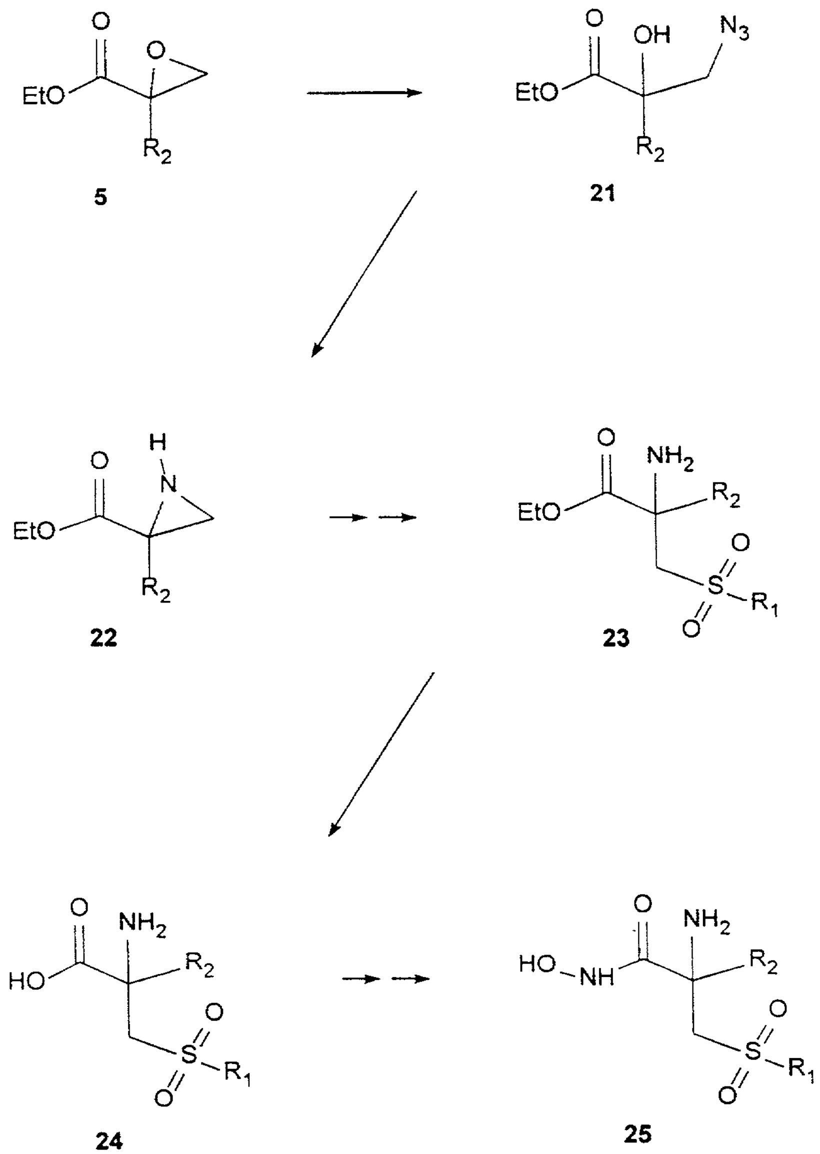
SCHEME IV



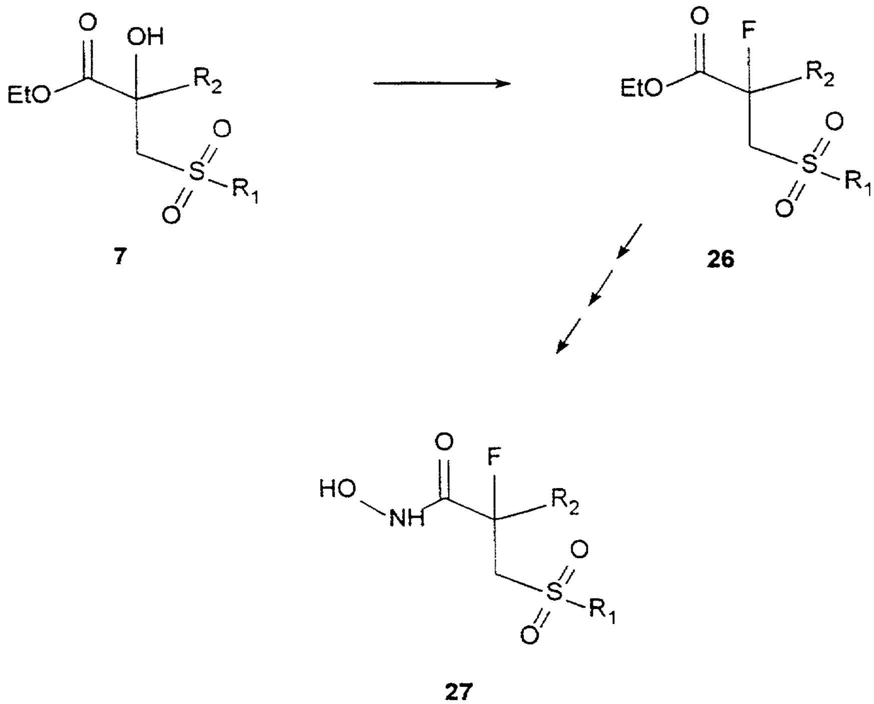
SCHEME V



SCHEME VI



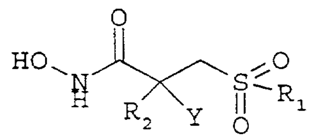
SCHEME VII



CLAIMS

We claim:

1. A compound of formula I



I

or pharmaceutical acceptable salts thereof wherein:

R_1 is

a) C_{4-12} alkyl,

b) C_{4-12} alkenyl,

c) C_{4-12} alkynyl,

d) $-(CH_2)_h-C_{3-8}$ cycloalkyl,

e) $-(CH_2)_h$-aryl,

f) $-(CH_2)_h$-het,

R_2 is

a) C_{1-12} alkyl,

b) C_{2-12} alkenyl,

c) C_{2-12} alkynyl,

d) $-(CH_2)_h-C_{3-8}$ cycloalkyl,

e) $-(CH_2)_h-C_{3-8}$ cycloalkenyl,

f) $-(CH_2)_h$-aryl,

g) $-(CH_2)_h$-het,

h) $-(CH_2)_h$-Q,

i) $-(CH_2)_i$-Q or $-(CH_2)_i-X-R_4$, optionally the $-(CH_2)_i-$ chain can be substituted with one or two C_{1-4} alkyl or phenyl, which in turn can be substituted with one to three halo or C_{1-4} alkyl, or

l) $-(CH_2)_hCHR_5R_6$;

R_3 is

a) H,

b) C_{3-6} cycloalkyl,

c) C_{1-4} alkyl, or

d) $-(CH_2)_h$-phenyl;

X is

a) -O-,

b) -S(=O)j-,

c) $-NR_7-$,

d) $-S(=O)_2NR_8-$, or

e) -C(=O)-;

R_4 is

a) H,

b) C_{1-8} alkyl,

c) $-(CH_2)_h$-phenyl, or

d) $-(CH_2)_h$-het;

R_5 is

a) C_{1-4} alkyl, or

b) $-C(=O)R_3$;

R_6 is

a) $-C(=O)R_3$, or

b) $-(CH_2)_hC(=O)R_3$;

R_7 is

a) H,

b) C_{1-4} alkyl,

c) $-(CH_2)_h$-phenyl,

d) $-C(=O)-R_3$,

e) $-S(=O)_2R_3$, or

f) $-C(=O)OR_3$;

R_8 is

a) C_{1-4} alkyl, or

b) $-(CH_2)_h$-phenyl;

Y is

a) -OH,

b) $-NR_9R_{10}$, or

c) fluoro;

R_9 and R_{10} are the same and different and are

a) H,

b) $-C(=O)-R_3$,

c) $-C(=O)-OR_3$, or

d) $-C(=O)-NHR_3$;

aryl is monocarbocyclic, or bicarbocyclic aromatic moiety;

het is 5- to 10-membered unsaturated monomonocyclic or bicyclic heterocyclic moiety having one to three atoms selected from the group consisting of oxygen, nitrogen, and sulfur;

Q is 5- to 10-membered saturated monocyclic or bicyclic heterocyclic moiety having one to two atoms selected from the group consisting of oxygen, nitrogen, and sulfur;

aryl, het, C_{1-12} alkyl, C_{1-4} alkyl C_{2-12} alkenyl, C_{2-12} alkynyl, -C_{3-8} cycloalkyl, -C_{3-8} cycloalkenyl, Q and phenyl being optionally substituted;

h is 0, 1, 2, 3, 4, 5, or 6; i is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; j is 0, 1, or 2; and with the following provisos:

a) where R_2 is C_{1-6} alkyl, Y is other than -NR_9R_{10},

b) where *h* is 0. het is attached to the α-position via carbon atom of heterocyclic moiety, and

c) where *h* is 0, Q is attached to the α-position via carbon atom of heterocyclic moiety.

2. A compound of formula I according to claim 1 wherein

R_1 is

a) C_{4-10} alkyl,

b) -$(CH_2)_h$-aryl, or

c) -$(CH_2)_h$-aryl substituted with C_{1-4} alkyl, C_{1-4} alkoxy, phenyl, 4-chlorophenyl, O-phenyl, het, O-het, halo, -NO_2, -CF_3, -CN, or -$N(C_{1-4}$ alkyl$)_2$;

R_2 is

a) -$(CH_2)_h$-Q, or $C(CH_3)_2$-Q or

b) -$(CH_2)_i$-X-R_4, $C(CH_3)_2$-X-R_4 ;

X is

a) -$S(=O)_j$-,

b) -NR_7-;

R_4 is

a) H,

b) C_{1-8} alkyl,

c) -$(CH_2)_h$-phenyl,

d) -$(CH_2)_h$-phenyl substituted with one to three C_{1-4} alkyl, C_{1-4} alkoxy, phenyl, C_{1-4} phenoxy, het, halo, -NO_2, or -CN, or

e) -$(CH_2)_h$-het;

R_7 is

a) -C(=O)-R_3;

Y is

a) -OH;

R_3, aryl, het, Q, *h*, *i*, *j* are as defined above, and with the proviso that where *h* is 0, Q is attached to the α -position via carbon atom of heterocyclic moiety.

3. A compound of formula I according to claim 1 wherein

R_1 is

a) $-(CH_2)_h$-phenyl, or

b) $-(CH_2)_h$-phenyl substituted with C_{1-4} alkoxy, phenyl, 4-chlorophenyl, O-phenyl, O-(pyrid-4-yl) or halo;

R_2 is

a) $-(CH_2)_i-S(=O)_2-R_4$, or

b) $-(CH_2)_i-NHR_7$;

R_4 is

a) C_{1-8} alkyl,

b) $-(CH_2)_h$-phenyl, or

c) $-(CH_2)_h$-phenyl substituted with one to three C_{1-4} alkyl, C_{1-4} alkoxy, phenyl, C_{1-4} phenoxy, or halo;

R_7 is

a) $-C(=O)C_{1-4}$ alkyl,

b) $-C(=O)C_{3-6}$ cycloalkyl,

c) $-C(=O)(CH_2)_h$-phenyl, or

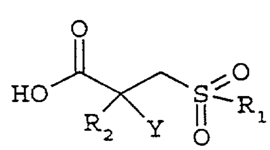
d) $-C(=O)-(CH_2)_h$-phenyl substituted with one to three C_{1-4} alkyl, C_{1-4} alkoxy, or halo;

Y is

a) -OH;

and *h* and *i* are as defined above.

4. A compound of formula 8



8

or pharmaceutical acceptable salts thereof wherein R_1 , R_2 and Y are as defined in claim 1.

5. A compound of claim 1 which is

N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-phenylbenzenesulfonyl)-propionamide,

N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-fluorobenzenesulfonyl)-propionamide,

N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-n-butylbenzenesulfonyl)-propionamide,

N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-methoxybenzenesulfonyl)-propionamide,

N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(N-benzenecarbonylamino)-propionamide,

N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-[N-(cyclopentylcarbonyl)amino]-propionamide,

N-Hydroxy-2-hydroxy-2-[(4-methoxybenzenesulfonyl) methyl]-3-(N-(4-methoxybenzenecarbonyl)amino)-propionamide,

N-Hydroxy-2-hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-(4-methoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-methoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-(4-butoxy-benzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-(4-butoxy-benzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-butoxy-benzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(methylthio)methyl-3-(4-butoxybenzenesulfonyl)-propionamide;

N-Hydroxy-2-hydroxy-2-(phenylthio)methyl-3-(4-butoxybenzenesulfonyl)-propionamide;

N-Hydroxy-2-hydroxy-2-(benzylthio)methyl-3-(4-butoxybenzenesulfonyl)-propionamide;

N-Hydroxy-2-hydroxy-2-(pyrid-2-yl)thiomethyl-3-(4-butoxybenzenesulfonyl)-propionamide;

N-Hydroxy-2-hydroxy-2-(2-methyl-5-oxo-6-hydroxy-2,5-dihydro-1,2,4-triazin-3-yl)thiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(2-aminothiazol-5-yl)thiomethyl-3-(4-butoxy-benzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(2-methyl-1,3,4-thiadiazol-5-yl)thiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methyl-1H-imidazol-2-yl)thiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methyltetrazol-5-yl)thiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(tetrazolo[1,5-b]pyridazin-6-yl)thiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(pyrid-2-yl)methylthiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methyl-1H-imidazol-2-yl)methylthiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-benzyl-1H-imidazol-2-yl)methylthiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(5-methylisoxazol-3-yl)methylthiomethyl-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(2-benzylthio-2-methylethyl)-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-[2-(pyrid-2-yl)thio-2-methylethyl]-3-(4-butoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-(4-chlorobiphenylsulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-(4-chlorobiphenylsulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-chlorobiphenylsulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(phenylthio)methyl-3-(4-chlorobiphenylsulfonyl)-propionamide;

N-Hydroxy-2-hydroxy-2-(benzylthio)methyl-3-(4-chlorobiphenylsulfonyl)-propionamide;

N-Hydroxy-2-hydroxy-2-(pyrid-2-yl)methylthiomethyl-3-(4-chlorobiphenylsulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(5-methylisoxazol-3-yl)methylthiomethyl-3-(4-chlorobiphenylsulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-[2-(1-methylhydantoin-3-yl)-2-methylethyl]-3-(4-chlorobiphenylsulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-[2-(pyrid-2-yl)thio-2-methylethyl]-3-(4-chlorobiphenylsulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-(4-phenoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-(4-phenoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-phenoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-benzylhydantoin-3-yl)methyl-3-(4-phenoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(phenylthio)methyl-3-(4-phenoxybenzenesulfonyl)-propionamide;

N-Hydroxy-2-hydroxy-2-(benzylthio)methyl-3-(4-phenoxybenzenesulfonyl)-propionamide;

N-Hydroxy-2-hydroxy-2-(pyrid-2-yl)methylthiomethyl-3-(4-phenoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methyl-1H-imidazol-2-yl)methylthiomethyl-3-(4-phenoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-[2-(1-methylhydantoin-3-yl)-2-methylethyl]-3-(4-phenoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-[2-(1-methyl-1H-imidazol-2-yl)thio-2-methylethyl]- (4-phenoxybenzenesulfonyl)propionamide;

N-Hydroxy-2-hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-[4-(pyrid-4-yl)-benzenesulfonyl]propionamide;

N-Hydroxy-2-hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-[4-(pyrid-4-yl)-benzenesulfonyl]propionamide;

N-Hydroxy-2-hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-[4-(pyrid-4-yl)benzenesulfonyl]propionamide;

N-Hydroxy-2-hydroxy-2-(phenylthio)methyl-3-[4-(pyrid-4-yl)benzenesulfonyl]-propionamide;

N-Hydroxy-2-hydroxy-2-(benzylthio)methyl-3-[4-(pyrid-4-yl)benzenesulfonyl]-propionamide;

N-Hydroxy-2-hydroxy-2-(2-benzylthio-2-methylethyl)-3-[4-(pyrid-4-yl)-benzenesulfonyl]-propionamide;

N-Hydroxy-2-hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-[4-(pyrid-4-yl)oxybenzenesulfonyl]propionamide or

N-Hydroxy-2-hydroxy-2-(benzylthio)methyl-3-[4-(pyrid-4-yl)oxybenzenesulfonyl]propionamide.

6. A compound of claim 4 which is:

2-Hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-(4-butoxybenzenesulfonyl)-propionic acid;

2-Hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-butoxybenzene-sulfonyl)propionic acid;

2-Hydroxy-2-(phenylthio)methyl-3-(4-butoxybenzenesulfonyl)propionic acid;

2-Hydroxy-2-(benzylthio)methyl-3-(4-butoxybenzenesulfonyl)propionic acid;

2-Hydroxy-2-(2-benzylthio-2-methylethyl)-3-(4-butoxybenzenesulfonyl)-propionic acid;

2-Hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-(4-chlorobiphenylsulfonyl)-propionic acid;

2-Hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-(4-chlorobiphenylsulfonyl)-propionic acid;

2-Hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-chlorobiphenyl-sulfonyl)propionic acid;

2-Hydroxy-2-(phenylthio)methyl-3-(4-chlorobiphenylsulfonyl)propionic acid;

2-Hydroxy-2-(benzylthio)methyl-3-(4-chlorobiphenylsulfonyl)propionic acid;

2-Hydroxy-2-(pyrid-2-yl)thiomethyl-3-(4-chlorobiphenylsulfonyl)propionic acid;

2-Hydroxy-2-(5-methylisoxazol-3-yl)methylthiomethyl-3-(4-chlorobiphenyl-sulfonyl)propionic acid;

2-Hydroxy-2-[2-(1-methylhydantoin-3-yl)-2-methylethyl]-3-(4-chlorobiphenyl-sulfonyl)propionic acid;

2-Hydroxy-2-(2-benzylthio-2-methylethyl)-3-(4-chlorobiphenylsulfonyl)-propionic acid;

2-Hydroxy-2-(1-methylhydantoin-3-yl)methyl-3-(4-phenoxybenzenesulfonyl)-propionic acid;

2-Hydroxy-2-(1-butylhydantoin-3-yl)methyl-3-(4-phenoxybenzenesulfonyl)-propionic acid;

2-Hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-(4-phenoxybenzene-sulfonyl)propionic acid;

2-Hydroxy-2-(phenylthio)methyl-3-(4-phenoxybenzenesulfonyl)propionic acid;

2-Hydroxy-2-(benzylthio)methyl-3-(4-phenoxybenzenesulfonyl)propionic acid;

2-Hydroxy-2-[2-(1-methylhydantoin-3-yl)-2-methylethyl]-3-(4-phenoxy-benzenesulfonyl)propionic acid;

2-Hydroxy-2-[2-(1-methyl-1H-imidazol-2-yl)thio-2-methylethyl]- (4-phenoxy-benzenesulfonyl)propionic acid;

2-Hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-[4-(pyrid-4-yl)benzenesulfonyl]propionic acid;

2-Hydroxy-2-(phenylthio)methyl-3-[4-(pyrid-4-yl)benzenesulfonyl]propionic acid or

2-Hydroxy-2-(1,5,5-trimethylhydantoin-3-yl)methyl-3-[4-(pyrid-4-yl)oxybenzenesulfonyl]propionic acid.

7. A method of inhibiting excess matrix metalloproteinase which comprises administering to a patient in need thereof an effective amount of a compound of claim 1.

8. A method of claim 7 wherein matrix metalloproteinases comprises stromelysin, collagenase, and gelatinase.

9. A method of treating a human suffering from or susceptible to diseases involving connective tissue degradation which comprises administering to a patient in need thereof an effective amount of a compound of claim 1.

10. A method of claim 9 wherein the diseases related to connective tissue degradation are osteoarthrits, rheumatoid arthritis, septic arthritis, and osteopenias such as osteoporosis, tumor metastasis (invasion and growth), periodontitis, gingivitis, corneal ulceration, dermal ulceration, gastric ulceration, inflammation, or asthma.

11. The method of claim 7 wherein the effective amount of the compound of claim 1 is administered orally, parenterally, or topically in a pharmaceutical composition.

12. The method of claim 9 wherein the effective amount of the compound of claim 1 is administered orally, parenterally, or topically in a pharmaceutical composition.

13. The method of claim 7 wherein said compound is administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day.

14 The method of claim 9 wherein said compound is administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day.

15. A pharmaceutical composition which comprises an amount of the compound of claim 1 effective to inhibit excess matrix metalloproteinase and a pharmaceutically acceptable carrier.

16. A compound of claim 1 for for use as a medicament.

17. Use of a compound of claim 1 for the manufacture of a medicament for inhibiting excess matrix metalloproteinase in a human suffering from or susceptible to a diseases involving connective tissue degradation.

18. The use of claim 17 wherein matrix metalloproteinases comprises collagenases, stromelysins, or gelatinases.

19. The use of claim 17 wherein the disease related to connective tissue degradation is osteoarthrits, rheumatoid arthritis, septic arthritis, osteopenias such as osteoporosis, tumor metastasis (invasion and growth), periodontitis, gingivitis, corneal ulceration, dermal ulceration, or gastric ulceration.

Declaration, Power Of Attorney and Petition

WE (I) the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

ALPHA-HYDROXY, -AMINO AND -FLUORO DERIVATIVES OF BETA-SULPHONYL HYDROXAMIC ACIDS AS MATRIX METALLOPROTEINASES INHIBITORS (as amended)

the specification of which

☐ is attached hereto.

☐ was filed on __________ as Application Serial No. __________ and amended on __________ .

☒ was filed as PCT international application Number PCT/IB98/02154 on NOVEMBER 18, 1998, and was amended under PCT Article 19 on __________ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s)

Application No.	Country	Day/Month/Year	Priority Claimed
			☐ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No

We (I) hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

60/072,655	NOVEMBER 21, 1997
(Application Number)	(Filing Date)
(Application Number)	(Filing Date)

We (I) hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.	**Filing Date**	**Status (pending, patented, abandoned)**
PCT/IB98/02154	NOVEMBER 18, 1998	

And we (I) hereby appoint: Norman F. Oblon, Reg. No. 24,618; Marvin J. Spivak, Reg. No. 24,913; C. Irvin McClelland, Reg. No. 21,124; Gregory J. Maier, Reg. No. 25,599; Arthur I. Neustadt, Reg. No. 24,854; Richard D. Kelly, Reg. No. 27,757; James D. Hamilton, Reg. No. 28,421; Eckhard H. Kuesters, Reg. No. 28,870; Robert T. Pous, Reg. No. 29,099; Charles L. Gholz, Reg. No. 26,395; Vincent J. Sunderdick, Reg. No. 29,004; William E. Beaumont, Reg. No. 30,996; Robert F. Gnuse, Reg. No. 27,295; Jean-Paul Lavalleye, Reg. No. 31,451; Stephen G. Baxter, Reg. No. 32,884; Robert W. Hahl, Reg. No. 33,893; Richard L. Treanor, Reg. No. 36,379; Steven P. Weihrouch, Reg. No. 32,829; John T. Goolkasian, Reg. No. 26,142; Richard L. Chinn, Reg. No. 34,305; Steven E. Lipman, Reg. No. 30,011; Carl E. Schlier, Reg. No. 34,426; James J. Kulbaski, Reg. No. 34,648; Richard A. Neifeld, Reg. No. 35,299; J. Derek Mason, Reg. No. 35,270; Surinder Sachar, Reg. No. 34,423; Christina M. Gadiano, Reg. No. 37,628; Jeffrey B. McIntyre, Reg. No. 36,867; Paul E. Rauch, Reg. No. 38,591; William T. Enos, Reg. No. 33,128; and Michael E. McCabe, Jr., Reg. No. 37,182; our (my) attorneys, with full powers of substitution and revocation, to prosecute this application and to transact all business in the Patent Office connected therewith; and we (I) hereby request that all correspondence regarding this application be sent to the firm of OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C., whose Post Office Address is: Fourth Floor, 1755 Jefferson Davis Highway, Arlington, Virginia 22202.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

1-00 Martha A. WARPEHOSKI
NAME OF FIRST INVENTOR

Residence: 7600 Currylane
Portage, Michigan 49024 MI

Martha A. Warpehoski
Signature of Inventor

Citizen of: UNITED STATES

Post Office Address: SAME AS ABOVE

April 4, 2000
Date

2-00

Mark Allen MITCHELL
NAME OF SECOND JOINT INVENTOR

Mark Allen Mitchell
Signature of Inventor

April 4, 2000
Date

Residence: 1628 Dover Road
Kalamazoo, Michigan 49008 MI

Citizen of: UNITED STATES

Post Office Address: SAME AS ABOVE

3-00

Donald E. HARPER
NAME OF THIRD JOINT INVENTOR

Donald E Harper
Signature of Inventor

April 3, 2000
Date

Residence: 11520 Channel Drive
Plainwell, Michigan 49080 MI

Citizen of: UNITED STATES

Post Office Address: SAME AS ABOVE

4-00

Linda Louise MAGGIORA
NAME OF FOURTH JOINT INVENTOR

Linda L. Maggiora
Signature of Inventor

April 6, 2000
Date

Residence: 4400 Glenrose Terrace
Kalamazzo, Michigan 49008 MI

Citizen of: UNITED STATES

Post Office Address: SAME AS ABOVE

NAME OF FIFTH JOINT INVENTOR

Signature of Inventor

Date

Residence:

Citizen of:

Post Office Address: